Synthetic Methods and Application Based on Directed *ortho* Metalation and Suzuki Cross Coupling Strategies

by

MANLIO ALESSI

A thesis submitted to the Department of Chemistry

in conformity with the requirements for

the degree of Doctor of Philosophy

Queen's University

Kingston, Ontario, Canada

December, 2008

ABSTRACT

The Directed *ortho* Metalation reaction is described in Chapter 1 of this thesis with particular emphasis on its mechanism and synthetic potential. Chapter 2 contains a review of the D*o*M (Directed *ortho* Metalation) of pyridine systems and describes the conditions that allow the one-pot D*o*M (Directed *ortho*-Metalation)-Boronation-Suzuki-Miyaura cross coupling of pyridines **2.263a-c**, **2.351-2.53** (Table 2.9) bearing several DMGs (Directed Metalation Groups) including the synthetically versatile diethyl amide functionality without incurring into commonly observed self-condensation processes. The method avoids the tedious and uncertain isolation of the intermediate boronic acids while offering rapid access to synthetically valuable arylpyridines (**2.354a-s**, Table 2.9). Selected aryl pyridine carboxamides were used to demonstrate the D*o*M-DreM (Directed remote Metalation) nexus that furnishes substituted and isomerically diverse azafluorenones **2.380a-d** (Table 2.11) with high regioselectivity.

The previous discovery of the anionic *O*→*C* α-vinyl carbamoyl migration of carbamoyl stilbenes stimulated its application in the total synthesis of natural product isoprekinamycin, bearing the unusual diazo group. Chapter 3 of this thesis describes the efficient synthesis of the key stilbene derivative **3.113** and its structural variations whose conversion to the desired naphthols **3.143**, **3.144**, **3.153** and **3.169** (Table 3.3) is accompanied by extensive decomposition, thus terminating this approach to isoprekinamycin. A modified approach *via* ***Z*-3.271** (Scheme 3.54) gave the desired naphthyl carbamate intermediates **3.274** and **3.278** (Schemes 3.55 and 3.56, respectively) whose complex DreM reactions prevented the completion of the synthesis but remain under active investigation in our laboratories.

Previous studies of the D*o*M reaction of aryl tetra*methyl* phosphorodiamidate have shown that unpractical experimental conditions are necessary, thus limiting synthetic application. Chapter 4 of this thesis describes the results concerning the performance of the tetra*ethyl* phosphorodiamidate DMG under standard D*o*M and DreM conditions, anionic phospha-Fries rearrangement, 1,4 lateral migration, and Suzuki cross coupling which demonstrate synthetic utility and application in synthetic aromatic chemistry.

ACKNOWLEDGMENT

I would like to thank Professor Snieckus for his constant guidance during the course of my research at Queen's. Standing with me at the whiteboard or from remote places his heraldic role took him, he always found the way to dispense encouragements when progresses were sluggish to come or to share my excitement on rarer occasions. He was *a group member* whose waves rippled across the group, engaged minds and etched teachings well beyond chemistry and work ethics.

Many thanks also to the members of my committee, Dr. Lemieux and Dr. Stan Brown who critically reviewed my progresses during these years. Particular appreciation is also felt for the stimulating discussions I had with Dr. Brown and Dr. Alexei A. Neverov.

I am extremely grateful to Dr. Mark A. Reed who was an inspiring role model in the lab, companion of late hours at the fumehood and a mentor to whom I owe all my lab skills.

I am deeply indebted to Dr. Jignesh Patel who imparted a new momentum to the total synthesis of isoprekinamycin and for providing me, in the final part of my work, with lab equipment, fumehood space and, not least of all, a receptive ear in frustrating times.

Finally, a tribute should be expressed to the Snieckus group as a whole. Thank you to all the members that I have encountered in this journey, for sharing their chemical knowledge, their unwritten lab techniques learned in far regions of the world, their ideas and experience as well as their cultural differences and their friendship. I will not forget the constructive atmosphere that shrouded all of this, neither the capsized canoe. And one last thing: I am still not convinced that loud music does break alkyllthium aggregates.

STATEMENT OF ORIGINALITY

I (Manlio Alessi) hereby declare that I am sole author of this thesis.

All of the experiments described in this thesis, except where specifically indicated, were performed by the author under the supervision of Prof. Snieckus.

The following is a list of new compounds prepared using new methodology during the course of this work: **2.354a-d**, **2.354h-j**, **2.348b**, **2.354k-m**, **2.354s**, **2.380a-d**, **3.126**, **3.127**, **3.116**, **3.129**, **3.134-3.137**, **3.113**, **3.114**, **3.140-3.143**, **3.146**, **3.148-3.153**, **3.168**, **3.169**, **3.171**, **3.172**, **3.184a**, **3.208a**, **3.220**, **3.244**, **3.246-3.250**, ***E*-3.253**, **(*E*)-3.260**, **3.270-3.272**, **4.126a,b**, **4.127a-j**, **4.128**, **4.141-4.143**.

The following is a list of known compounds prepared using new methodology or existing methods during the course of this work: **2.380b,c**, **3.205**, **3.206**, **3.248**, ***Z*-3.255**, ***Z*-3.256**, **3.257**.

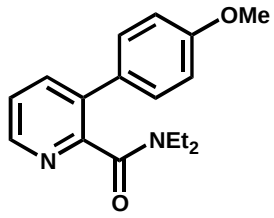
To Leanne and Matteo

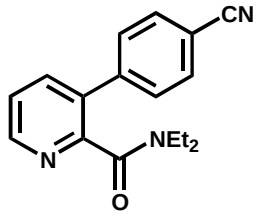
TABLE OF CONTENTS

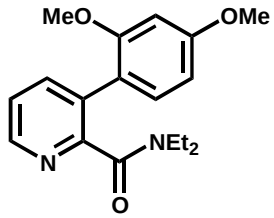
LIST OF TABLES

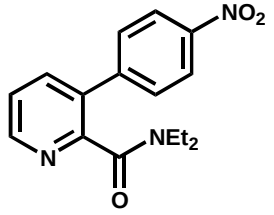
LIST OF FIGURES

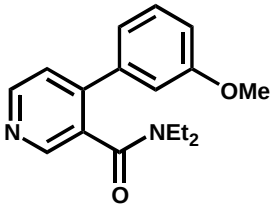
SPECIFIC EXPERIMENTAL PROCEDURES

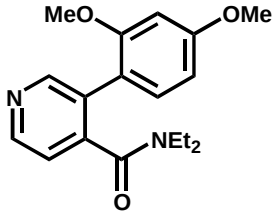


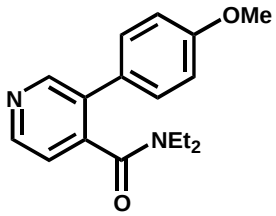


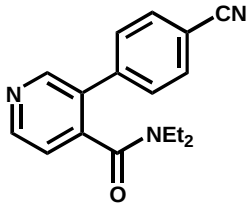


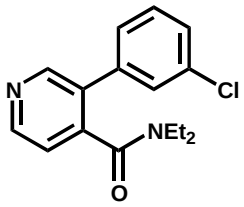


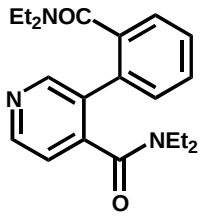


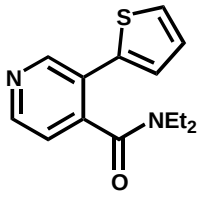


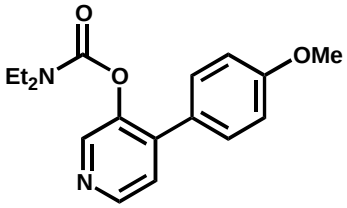


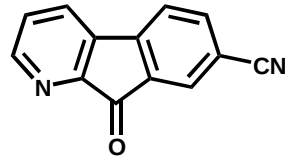


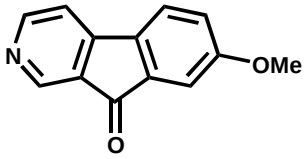


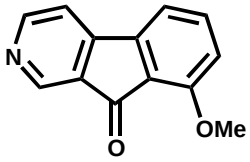


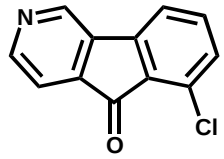


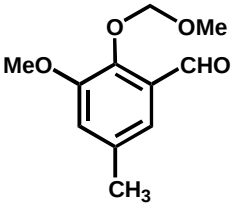


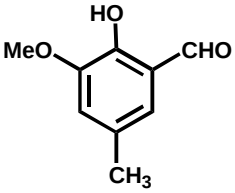


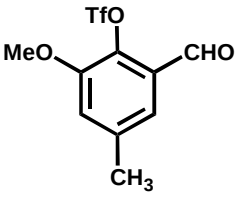


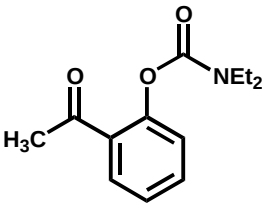


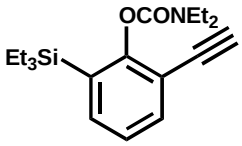


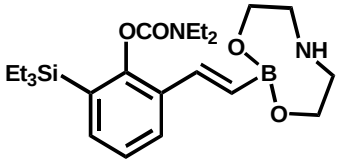


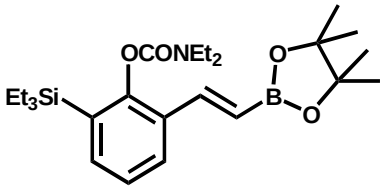


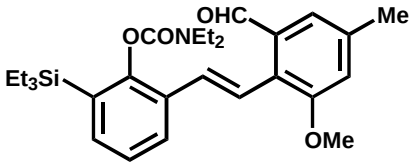


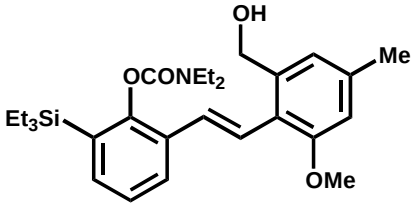


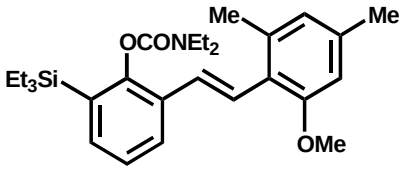


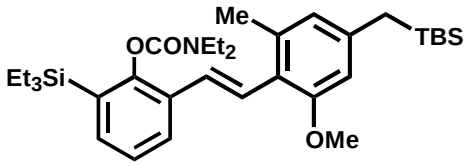


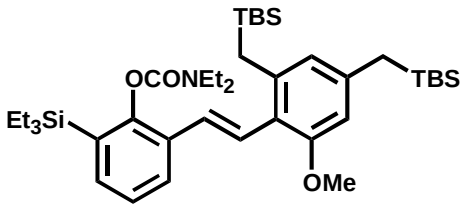


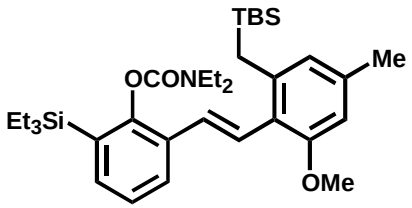


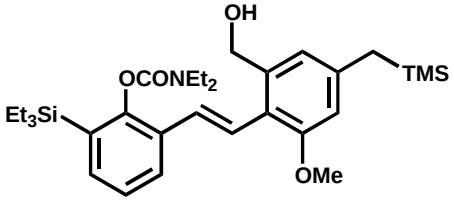


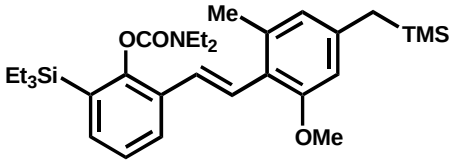


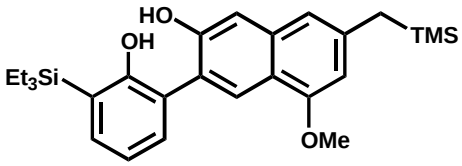


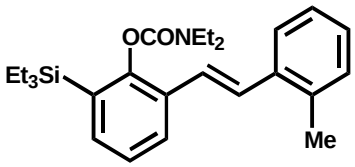


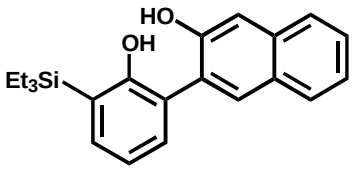


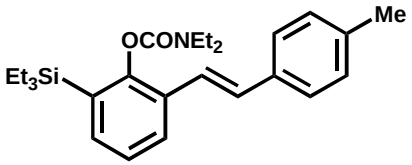


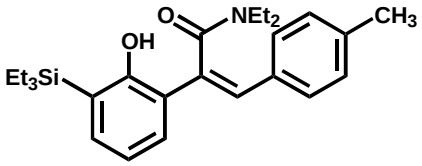


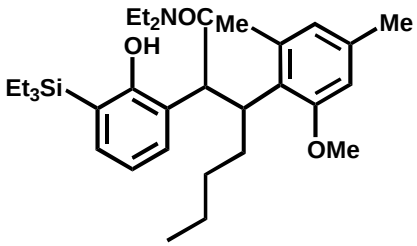


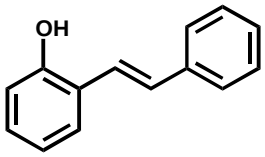


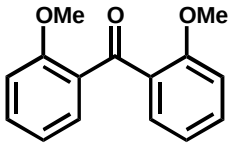


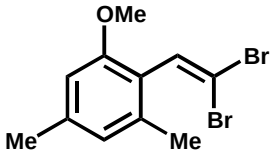


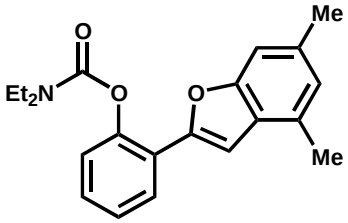


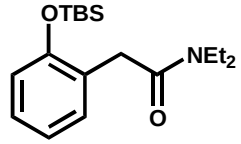


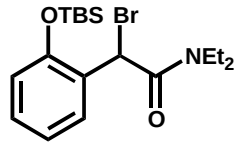


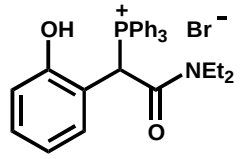


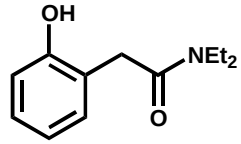


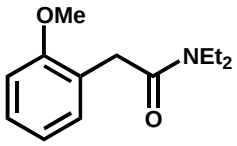


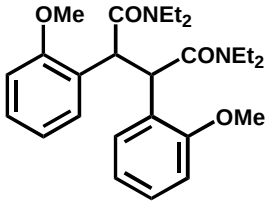


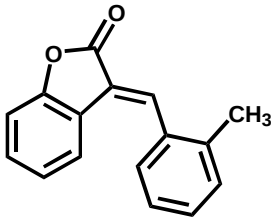


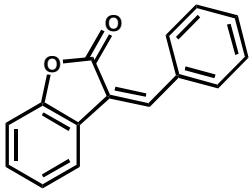


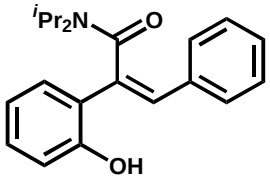


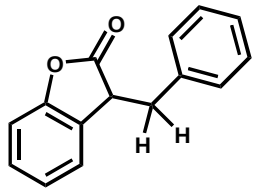


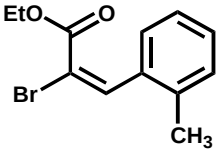


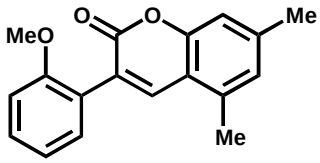


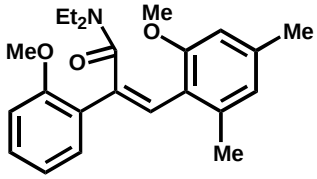


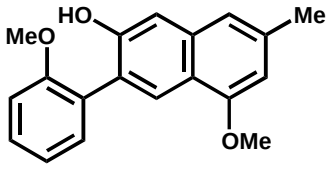


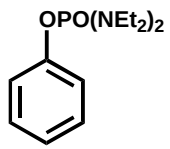


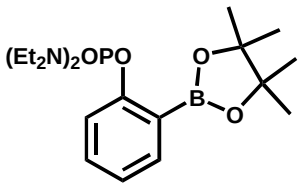


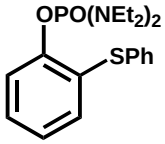


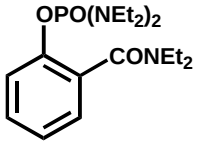


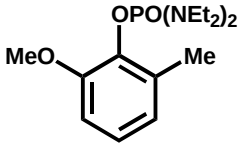


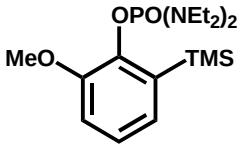


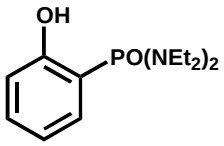












LIST OF ABBREVIATIONS

acac	acetylacetonyl
AIBN	2,2'-azo *bis*isobutyronitrile
BINOL	1,1'-bi-2,2'-naphthol
Boc	*t*-Butoxycarbonyl
Bpy	2,2'-bipyridyl
CAN	cerium(IV) ammonium nitrate
CIPE	complex-induced proximity effect
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,1-dichloroethane
DFT	density functional theory
DG	directing group
DIBAL	diisobutylaluminium hydride
DIPA	diisopropylamine
DMAP	*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMG	directed metalation group
DMSO	dimethylsulfoxide
D*o*M	directed *ortho* metalation
dppb	1,4-*bis*(diphenylphosphino)butane
dppp	1,3-*bis*(diphenylphosphino)propane
DreM	directed remote metalation
E^+	electrophile
EAS	electrophilic aromatic substitution
EDG	electron-donating group

EVL	ethoxyvinyllithium
EWG	electron-withdrawing group
FG	functional group
gCOSY	gradient-selected correlation spectroscopy
GSH	glutathione
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HOESY	heteronuclear Overhauser enhancement spectroscopy
IBX	*o*-iodoxybenzoic acid
Imes	1,3-*bis*(mesityl)-4,5-dihydroimidazol-2-ylidene
Ipr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
LDA	lithium diisopropylamide
LG	leaving group
LiC-KOR	butyllithium-potassium *tert*-butoxide
LiDMAE	lithium dimethylaminoethoxide
LiHMDS	lithium *bis*(trimethylsilyl)amide
LiTMDA	lithium *N*,*N*,*N*'-trimethylethylenediamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
LiNMP	lithium 1-methylpiperazide
MNDO	modified-neglect of diatomic overlaps
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
M-X	metal-halogen exchange
NBS	*N*-bromosuccinimide
NOESY	nuclear Overhauser enhancement spectroscopy
OA	oxidative addition
PCC	pyridinium clorochromate
PG	protecting group
PM3	parametric method 3
PMB	*p*-methoxybenzyl

PMDTA	*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine
POPd2	Dihydrogen di-μ-chlorodichlorobis (di-*tert*-butylphosphinito-*k*P)dipalladate(2-)
PPA	polyphosphoric acid
PTSA	*p*-toluene sulfonic acid
RCM	ring closing metathesis
SEM	2-(trimethylsilyl)ethoxymethyl
SET	single electron transfer
SiMes	1,3-*bis*(mesityl)-imidazol-2-ylidene
SM	starting material
S_NAr	nucleophilic aromatic substitution
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
S_RN1	radical-nucleophilic aromatic substitution
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEDI	1,1,3,3,-tetraethyl-1,3-disilaisoindolines
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
TFP	*tris*(2-furyl)phosphine
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
TMCDA	*N*,*N*,*N*',*N*'-tetramethyl-1,2-diaminocyclohexane
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TS	transition state
Ts	*p*-toluenesulfonyl
VNS	vicarious nucleophilic substitution

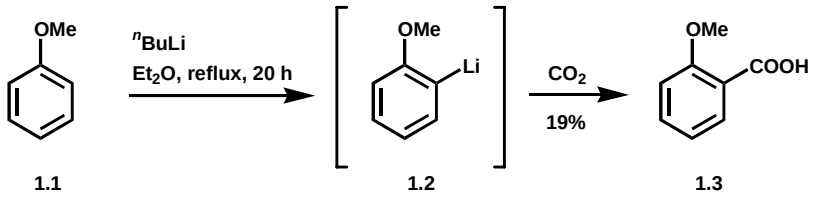
CHAPTER 1

The Directed *ortho* Metalation:

Mechanism, Developments and Applications

1.1. Introduction

The Directed *ortho* Metalation (D*o*M) reaction owes its origin to Gilman's[1] and Wittig's[2] independent discovery that anisole undergoes *ortho*-deprotonation using ^{n}BuLi and that a quench of the intermediate anionic species **1.2** with CO_2 affords, with high regioselectivity, albeit in 19% yield, 2-methoxybenzoic acid (Scheme 1.1). In the 65 years that followed, countless scientific papers have witnessed the constant development, the increasing mechanistic insight and, more recently, the industrial applications[3] of the D*o*M reaction. Since excellent reviews of this topic are available,[4] the discussion that follows will be limited to key features of the D*o*M, namely the Directed Metalation Groups (DMGs), suitable bases for this reaction and its mechanistic aspects.



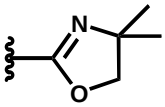
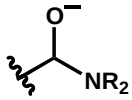
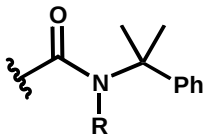
Scheme 1.1

1.1.1 Directed Metalation Groups (DMGs)

While benzene is relatively unreactive towards ^{n}BuLi,[5] the unexpected finding of Gilman and Wittig's was presumably due to the ability of the methoxy group to coordinate the alkyllithium and hold it in close proximity to the *ortho* hydrogen atoms (CIPE theory).

Like the methoxy group, DMGs must include a heteroatom for coordination purposes while being poorly electrophilic to resist attack by the strong base (a negative charge and steric hindrance are therefore positive qualities of a DMG). Selected DMGs, formally grouped in two classes, are shown in Table 1.1. According to the most accepted theory, applicable to most DMGs, the power of a directing group is a feature related to its coordination ability and is determined through inter- and intramolecular competition studies.[4a,6]

Table 1.1. Selected Directed Metalation Groups

Carbon-Based DMGs		Ref.	Heteroatom-Based DMGs		Ref.
CON^-R	Hauser, 1964	7a	SO_2N^-R	Hauser, 1968	7h
	Meyers, 1975 Gschwend, 1975	7b 7c	SO_2NR_2 OCH_2OCH_3	Hauser, 1969 Christensen, 1975	7i 7j
$CONEt_2$	Beak, 1977	7d	$NHCO^tBu$	Gschwend, 1979	7k
	Comins, 1982*	7e	$NHCOO^tBu$ $OCONEt_2$	Muchowski, 1980 Snieckus, 1983	7l 7m
COOH	Mortier, 1994	7f	$P(O)(^tBu)_2$	Snieckus, 1998	7n
	Snieckus, 1999	7g	OSO_2NR_2 $OCON(TMS)^iPr$	Snieckus, 2003 Hoppe, 2006*	7o 7p

* Generated in situ.

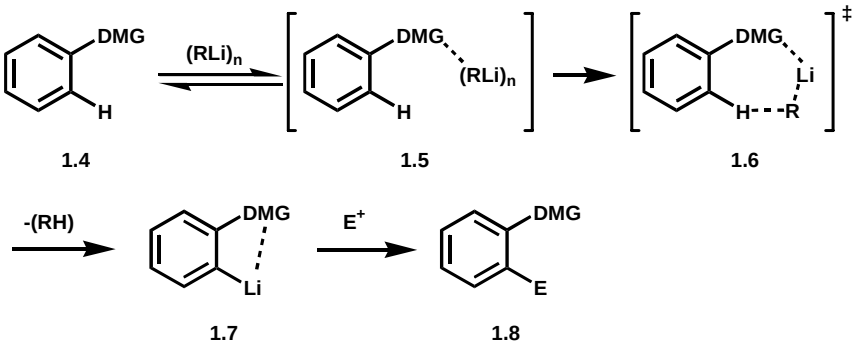
However, the extent of a DMG's synthetic application is mainly linked to its ability for conversion to other functionalities. For instance, the oxazoline moiety, a masking group for the carboxylic group, as well as the OMOM and the NHBoc group may easily be hydrolyzed[8a,b] whereas cumyl amides may be decumylated.[7g] Diethyl- sulfonamides,[9] sulfamates[7o] and carbamates[10] have been cross coupled with Grignard reagents and, in the case of the SO_2NEt_2 and $OCONEt_2$ groups, Ni(0)-catalyzed reductive cleavage with

^{i}PrMgBr has been achieved, making them useful latent DMGs.[9,10] Manipulation of the powerful diethyl- carbamate and carboxamide DMGs through cyclization and intramolecular migration reactions has abundantly proven their versatility in several total syntheses.[11] Furthermore, the Schwartz reagent has been recently shown to reduce aromatic amides[12a-c] and carbamates[12d] under mild conditions to aryl aldehydes and phenols, respectively, while trimethoxyloxonium tetrafluoroborate (Me_3OBF_4)[13] or triflic anhydride/EtOH[14] may be used to efficiently convert amides to methyl and ethyl esters, respectively. Interestingly, some unstable DMGs have been generated and used *in situ* as is the case of *α*-amino alkoxydes[15] and *N*-TMS-*N*-isopropyl carbamates[7p] which, upon mild hydrolysis, unveil the formyl and the hydroxyl groups, respectively. Finally, lithiated species with planar chirality, namely ferrocenes and (arene)tricarbonylchromium complexes, have been obtained using chiral DMGs,[16] chiral bases,[17] chiral additives[18] or their combination.[19] Arylcarboxamides displaying axial chirality (around the bond C_{aryl}-$CONR_2$) have also been obtained through addition of (−)-sparteine[20] or by lithiation of their enantiopure tricarbonyl(arene)chromium complexes with achiral bases.[21]

1.1.2 Mechanism

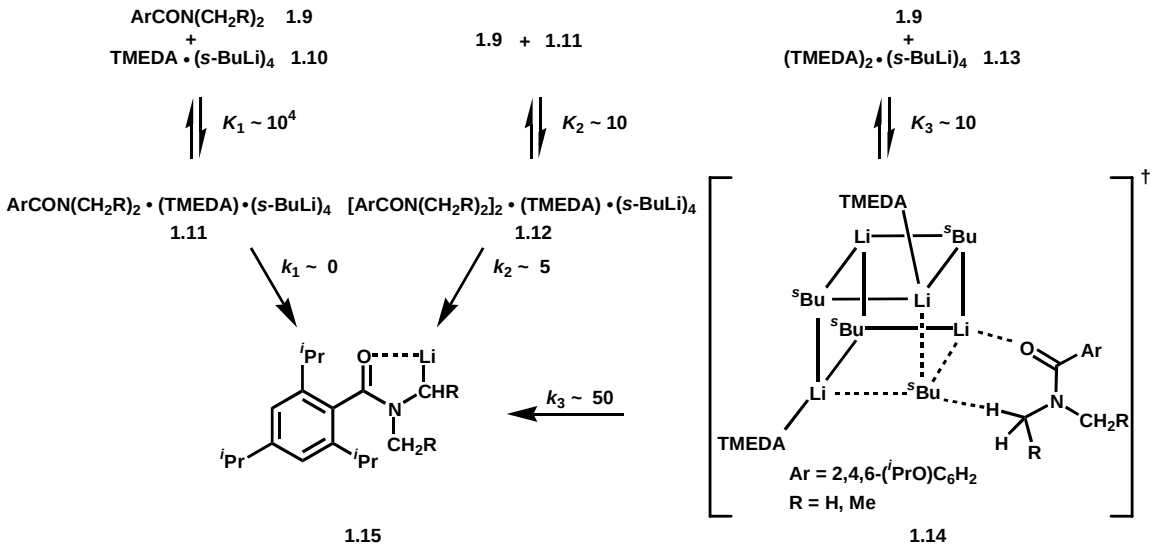
The most accepted mechanism of the D*o*M can be reduced to a three-step sequence beginning with the rapid equilibrium coordination of the alkyllithium aggregate to a heteroatom or hetero group of the DMG (**1.5**, Scheme 1.2). In a slow, but irreversible process, this aggregate evolves towards a coordinated *ortho*-lithiated species **1.7** which, upon quench with an electrophile, affords, in the simplest of cases, a 1,2-disubstituted aromatic product **1.8**. The hypothesis of an initial DMG-base coordination is the basic feature of the so called complex-induced proximity effect (CIPE), a concept introduced in

1985 by Beak, Meyers[22] and subsequently by Klumpp,[23] suggesting that a prelithiation event might bring reactive groups into proximity before the occurrence of the actual reaction.



Scheme 1.2

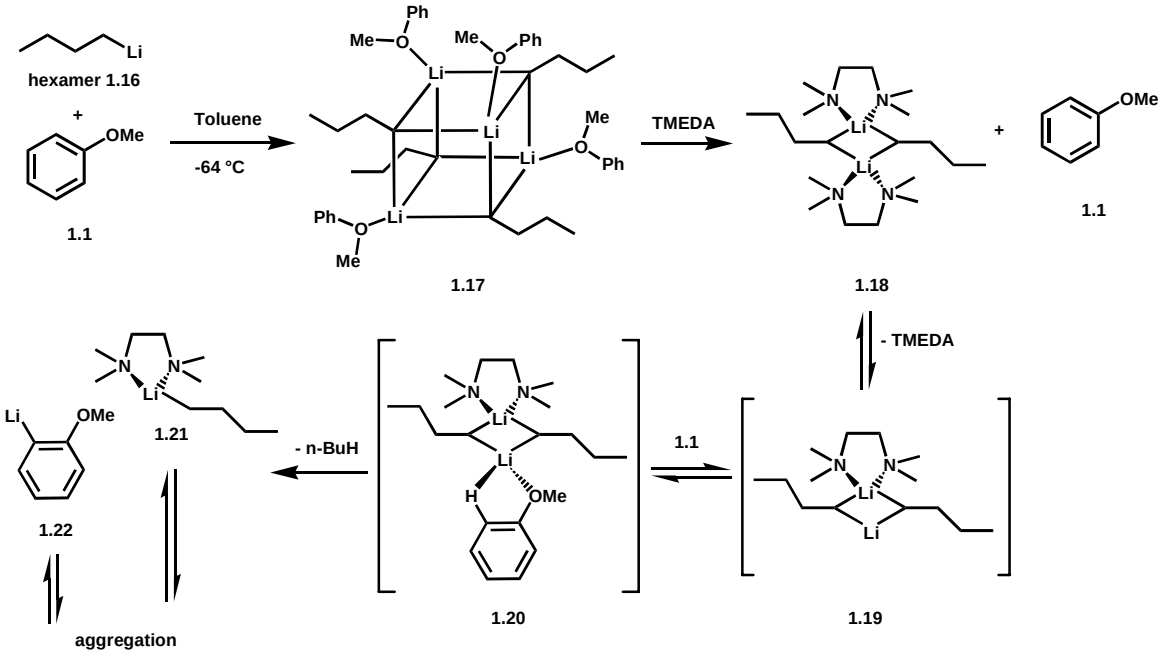
Despite the many observations supporting this theory, indisputable evidence of this mechanism is yet to be found. Among the kinetic data supporting the intervention of a prelithiation complex,[24] Beak's authoritative study on the α′-metalation of *N*,*N*,-dialkylbenzamides **1.9** (Scheme 1.3) with ^{s}BuLi/TMEDA, exceptionally includes the monitoring of such a complex through stopped-flow IR spectroscopy.[25] A reaction scheme consistent with Beak's data rules out the reaction of a single complex. Instead, it involves multiple coordination equilibria generating three $(amide)_x(TMEDA)_y(^{s}BuLi)_4$ complexes (x and y = 1,2) **1.11**, **1.12**, **1.14** which, as the number of ligands on the ^{s}BuLi tetramer increases, have less favourable equilibria of formation but higher reactivity in the *ortho*-lithiation process (k = 0, 5, 50 respectively, Scheme 1.3). In the most reactive complex **1.14,** the three-fold ligand association destabilizes the aggregate and favours a reaction between the now labile carbanion and the α′-proton. Unfortunately, these studies were carried out in hydrocarbon solvents and the conclusions cannot be easily extended to most lithiation reactions which are performed in ethers.



Scheme 1.3

Schleyer has observed the prelithiation coordination complex **1.17** (Scheme 1.4) through ^{6}Li,^{1}H HOESY experiments in the metalation of anisole with ^{n}BuLi (again in non-ethereal solvent, Scheme 1.4).[26] Despite the tight contact between lithium and the *ortho* hydrogen atoms of anisole, this complex was found to be unproductive and underwent disaggregation upon addition of TMEDA as a result of its higher affinity for the base.[27] Only at this stage does free anisole begin to be metalated by a hypothetical species (^{n}BuLi)$_2$•TMEDA (**1.19**) and thence proceeds to another hypothetical prelithiation complex (**1.20**). The existence of *ortho*-lithiated species like **1.22** is supported by considerable experimental evidence, and several crystal structures of their aggregates confirm a high degree of heteroatom-lithium interaction.[28] The competitive *ortho* lithiation of a series of structurally related amides shows that the DMG's efficiency increases with decreasing dihedral angle between the *ortho*-H atom and the carbonyl group, thus supporting the hypothesis that the proximity of the carbonyl oxygen atom

(and presumably the base coordinated to it) to the *ortho* proton is paramount to an effective lithiation (Fig. 1.1).[29] These results were taken as inferential proof of CIPE.



Scheme 1.4

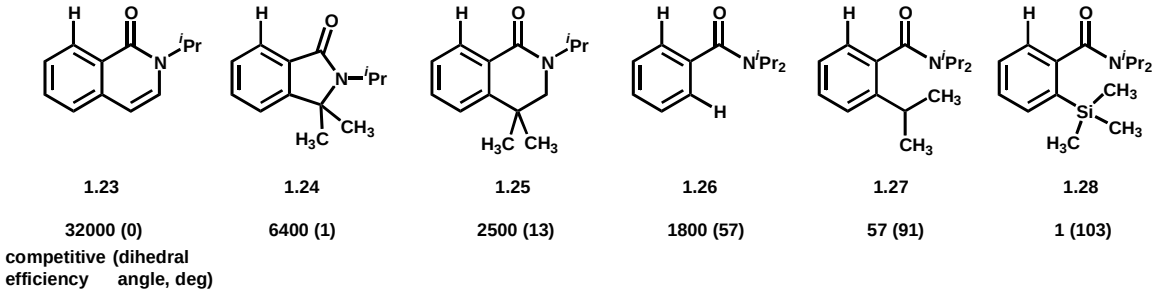
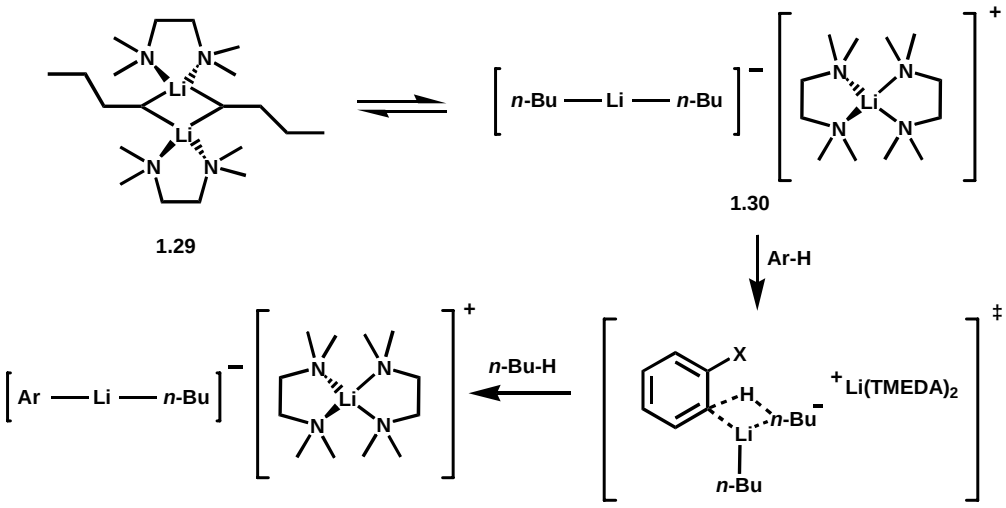


Figure 1.1 Relationship Between Competitive *ortho* Lithiation of Amides and their CO/*o*-H Dihedral Angle

Collum's group has also contributed to the study of the D*o*M mechanism with particular attention to the role of TMEDA.[30] In a kinetic study on the ^{n}BuLi/TMEDA *ortho*-metalation of 5 aromatic substrates, (benzene, anisole, 1,3-$(MeO)_2C_6H_4$, $MeOCH_2OC_6H_5$

and $Me_2NCH_2CH_2OC_6H_5$), Collum challenged the very assumption that ortholithiation is directed, at least in the meaning that CIPE implies.[30b] This doubt was fueled by the finding that these processes could be described by 5 analogous substituent-dependent rate laws but one substituent-independent mechanism which includes a rate limiting transition state of stoichiometry $[(^nBuLi)_2(TMEDA)_2(Ar\text{-}H)]^{\ddagger}$. Such common TS cannot explain the *ortho*-lithiation of substrates so different in their coordinative ability, unless the Li-O complexation is not a relevant feature of it (**1.31**, Scheme 1.5). It follows that the regioselectivity of the lithiation process must depend largely on other factors which, according to calculations, are suggested to be inductive effects of the ring substituent(s). Collum has invoked the involvement of the triple ion **1.30** whose stability is supported by *ab initio* computational studies and crystallographic data for related species.[31]



Scheme 1.5

However, extension of this theory to the metalation of substrates other than those studied by Collum is not straightforward, especially when inductive effects and coordinative abilities of the substituents are very different from those discussed here, as is the case of

carboxamides. Indeed, two recent articles by the same author reporting detailed kinetic and structural studies on the anionic Snieckus-Fries rearrangement of aryl carbamates have recognized the formation of precomplexes.[32] Through a judicious choice of *meta*-substituents, Collum was able to monitor (React-IR) and characterize (^{6}Li, ^{13}C, ^{15}N NMR spectroscopy) stable representatives for all lithiated intermediates of this anionic reaction (Scheme 1.6). Thus, the rate limiting *ortho*-lithiation of **1.33a** followed by a rapid Fries rearrangement to **1.44a** (no buildup of **1.35a** or **1.40a** was detected), follows the rate law

$$-d[\mathbf{1.33a}]/dt = k'[\mathbf{1.33a}][\mathrm{LDA}]^{1/2}[\mathrm{THF}]^{0} \qquad \text{(eq. 1)}$$

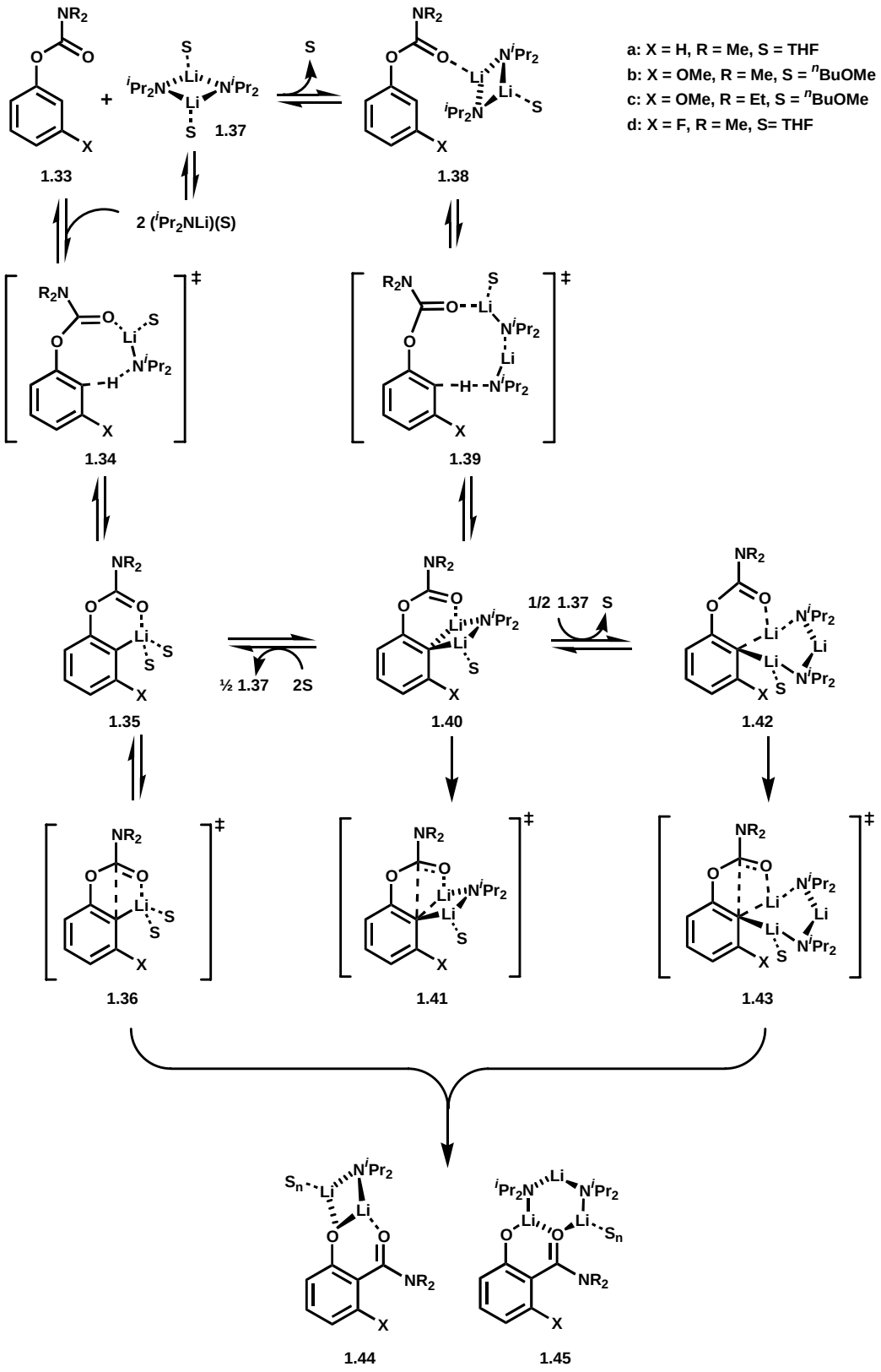
consistent with a mechanism involving the monomer-based TS **1.36a** (Scheme 1.6). On the other hand, the precomplex **1.38b** was observed to quantitatively form in poorly coordinating solvents such as ^{t}BuOMe and ^{n}BuOMe. Thanks to the stabilizing inductive effect of the fluorine substituent (the OMe group has a similar effect), **1.38b** was observed to convert to **1.40b** following the rate law

$$-d[\mathbf{1.38b}]/dt = k'[\mathbf{1.38b}][\mathrm{LDA}]^{0}[^{n}\mathrm{BuOMe}]^{0} \qquad \text{(eq. 2)}$$

which is consistent with the intermediacy of the dimer-based TS **1.39b**. The following carbamoyl migration step was studied, in the same solvent, on the diethyl analogue **1.40c** and was found to follow the rate law

$$-d[\mathbf{1.40c}]/dt = k'[\mathbf{1.40c}][^{n}\mathrm{BuOMe}]^{-1}[\mathrm{LDA}]^{1/2} + k''[\mathbf{1.40c}][^{n}\mathrm{BuOMe}]^{0}[\mathrm{LDA}]^{0} \qquad \text{(eq. 3).}$$

The inverse dependence on the ^{n}BuOMe concentration indicates a mechanism involving solvent dissociation (**1.40c** + **1.37** → **1.42c** + **Solvent**) while the second component of the equation suggests a non dissociative mechanism. Thus, the only observed intermediate **1.40c** may evolve towards TS **1.41c** and **1.43**, both deemed viable by DFT calculations.


a: X = H, R = Me, S = THF
b: X = OMe, R = Me, S = nBuOMe
c: X = OMe, R = Et, S = nBuOMe
d: X = F, R = Me, S= THF
1.33
1.37
1.38
2 (iPr2NLi)(S)
1.34
1.39
1.35
1.40
1.42
½ 1.37 2S
1/2 1.37 S
1.36
1.41
1.43
1.44
1.45

Scheme 1.6

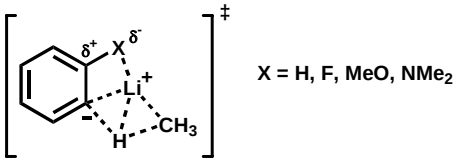
Similarly, the conversion of **1.40d**[33] to **1.44d** is described by

$$-d[\mathbf{1.40d}]/dt = k'[\mathbf{1.40d}][\mathrm{LDA}]^{-1/2}[\mathrm{THF}]^2 + k''[\mathbf{1.40d}][\mathrm{LDA}]^0[\mathrm{THF}] \qquad \text{(eq. 4)},$$

once again suggesting two parallel reaction pathways, one leading to **1.36d** following dissociation of **1.40d** to **1.35d** (*i.e.*, a monomer-based rearrangement inhibited, as indicated by the reverse dependence, by LDA) and a distinct mixed dimer-based rearrangement (**1.40d** → **1.41d**). Collum has also studied the effects of several other solvents on the reaction pathway of the Snieckus-Fries rearrangement. Strongly coordinating solvents such as HMPA and TMCDA foster the formation of reactive monomeric lithiated intermediates (**1.35**) while the weakly coordinating Me_2NEt and the strongly coordinating, but hindered TMEDA give mixtures of mixed-dimer and mixed-trimers (**1.40** and **1.42**). Amongst the ethereal solvents, while ^{n}BuOMe furnishes exclusively mixed-dimers, the strongly coordinating DME and THF can give monomers and dimers or exclusively the latter if excess of LDA is used. Far from being mere curiosities, Collum's results are a useful magnifying lens on the Snieckus-Fries rearrangement which can now be viewed as a sequence of cascading yet controllable reaction steps. To illustrate, where the carbamoyl migration is undesired, the exploitation of solvent effects may be an alternative option to the use of hindered carbamates and low temperatures. The zeroth-order THF dependence of the ortholithiation step (eq. 1) together with the second-order THF dependence of the carbamoyl migration (eq. 4) suggests that lower dilutions will inhibit the Fries rearrangement. A similar result may be obtained with the use of poorly coordinating solvents (^{n}BuOMe, eqs. 2 and 3).

After the seminal publication of 1989 in which the reversible prelithiation complex **1.20** (Scheme 1.4) was proposed and supported by MNDO calculations, Schleyer has

embraced a new theory which rejects CIPE as a relevant aspect of the D*o*M reaction and postulates one four-center TS (**1.46** Fig. 1.2) as the only event between reactants and products.[34] Schleyer's argument is based on the criticism that a weakly bound complex, if it existed, should leave most of the substrate uncoordinated and therefore free to react with little selectivity. On the contrary, a tight complex, while ensuring high regioselectivity, must overcome a higher activation energy to reach the transition state so that, contrary to the observations, regioselectivity should be accompanied by lower reactivity.



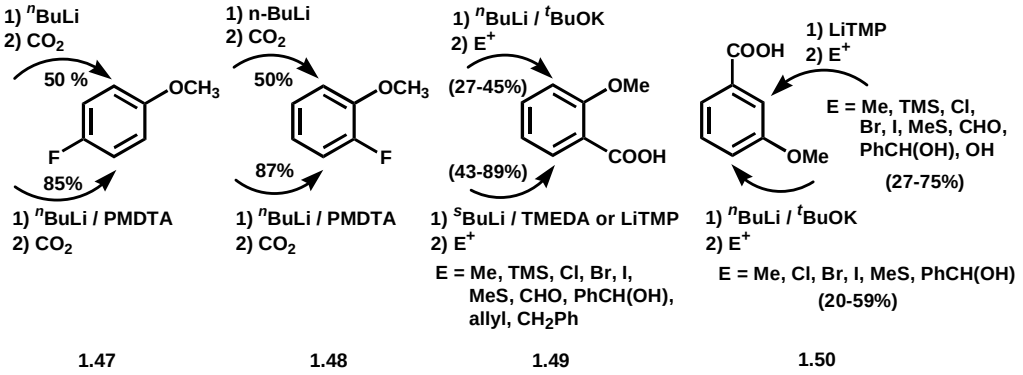
1.46

Figure 1.2 Four-Center TS Postulated by Schleyer for the D*o*M Reaction

In Schleyer's model, directing and accelerating effects of the DMG are due to the strong stabilization of the transition state, rather than to a prelithiation complex which has led his suggestion to replace the term "complex-induced proximity effect" with the more accurate "kinetically enhanced metalation". High level calculations performed on the general TS structure **1.46**, place the "active" lithium and the coordinating atom of the DMG in the same plane as the ring (less so for the bulkier dimethylamino DMG) and within shorter distance than in the corresponding hypothetical precomplex. This factor, together with the stabilizing alternation of opposite charges, was invoked to explain the low computed activation energies for the *ortho*-lithiation.

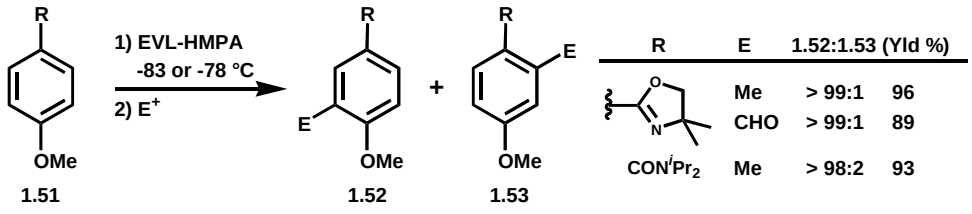
It is intuitive that inductive effects should have some role in the metalation of arenes by acidifying the hydrogens in the vicinity of an electron-withdrawing DMG. The high inductive effect and poor complexating ability of fluorine, chlorine and the trifluoromethyl group have allowed direct observation of this role. The metalation of $CF_3C_6H_5$ with ^{n}BuLi in Et_2O followed by CO_2 quench yields 24% of 2-trifluoromethyl benzoic acid and only 9% and 0.2% of the *meta* and *para* isomers respectively.[35] The more activated fluorobenzene under similar conditions undergoes only *ortho*-deprotonation,[36] and, if subjected to intermolecular competition against chlorobenzene, is 8 times more reactive towards ^{s}BuLi and 20 times towards LiTMP.[37] In intramolecular lithiation competition experiments, fluorine was found to outperform all other halogens[38] and the CF_3 group[39] as DMG. The inductive effects can be advantageously exploited in the metalation of aromatic substrates bearing two heteroatom-based DMGs. Schlosser has screened large libraries of haloarenes[40] and experimentally found that "optionally site selectivity" can be achieved in most cases with a careful choice of base and ligand. As an example, 2-, and 4-fluoroanisole (**1.48** and **1.47**, Scheme 1.7 but also the corresponding OMOM-bearing analogs), are deprotonated exclusively *ortho* to the ether group when ^{n}BuLi is used and *ortho* to fluorine when this base is precomplexed with ^{t}BuOK (Lochmann-Schlosser superbase also known as LIC-KOR) or *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (PMDTA).[41] The basis of this tunable selectivity is that weakly solvated organolithium reagents preferentially exploit the coordinative ability of a DMG and react by CIPE, whereas fully complexed bases (like ^{t}BuOK or PMDTA) do not compete for other ligands and selectively target those positions where the negative charge

can be most efficiently stabilized.[42] A recent application of these effects has been demonstrated by Mortier on methoxy benzoic acids **1.49** and **1.50** (Scheme 1.7).[43]



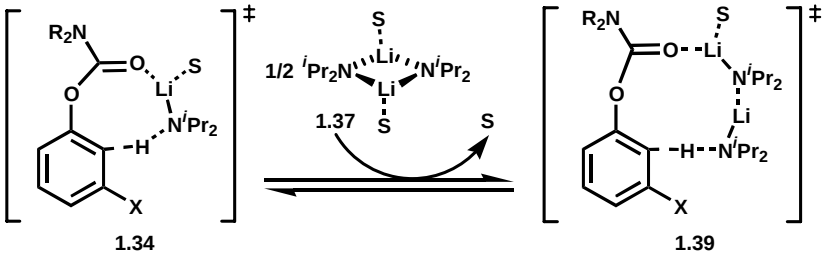
Scheme 1.7

A similar site selection was achieved by Meyers in the metalation of anisoles **1.51** and their positional isomers which, despite the expectations based on the directing power of the oxazoline, are deprotonated *ortho* to the MeO group when using the ethoxyvinyllithium-HMPA base (EVL-HMPA, Scheme 1.8).[44] This deprotonation was proven to be a kinetically controlled event which was rationalized by steric effects created by a large cluster of EVL and HMPA. Despite its unknown stoichiometry, the cluster's unique topography may prevent metalation *ortho* to large, albeit strong DMGs while allowing productive interactions with weak but smaller directing groups.



Scheme 1.8

In summary, while the "kinetically enhanced metalation" is buttressed only by calculations,[34,45] regioselectivity can be realistically rationalized through inductive effects enhancing hydrogen acidity. The CIPE-based mechanism is also based on considerable experimental evidence for the D*o*M reaction. Collum has spectroscopically (React-IR) observed the precomplex **1.38b** in ^{n}BuOMe and has obtained kinetics consistent with its direct conversion to **1.40b** as well as convincing DFT data for the rate limiting TS **1.34** and **1.39** (Scheme 1.6). Nevertheless, he does not see precomplexes as critical intermediates to the preorganization of the species undergoing reaction. Rather, he reasons that, whether or not a reaction follows a monomer- or a dimer-based pathway (**1.34** vs. **1.39**, Scheme 1.9) ultimately depends on the energetic cost of the solvent dissociation which affects observable complexation in exactly the same way. In other words, the trimeric character of **1.39** is not a consequence of **1.38**, but they are both the result of the same underlying variable, solvent dissociation.[32b]

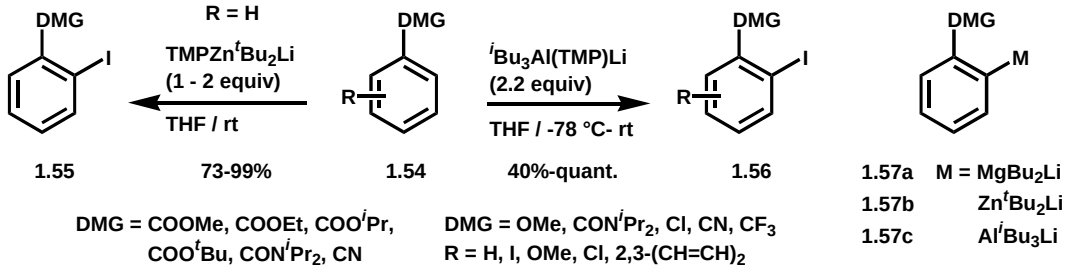


Scheme 1.9

1.1.3 Bases for the D*o*M Reaction

The large majority of D*o*M protocols involve the use of alkyllithiums alone or in combination with a bidentate ligand (generally TMEDA) capable of breaking down the hexameric (in hydrocarbon solvents) or tetrameric aggregates (in coordinating solvents) spontaneously formed by alkyllithiums to monomers or dimers with significant

amplification of their basicity.[46] While the kinetic basicity of LDA and LiTMP is insufficient to achieve the deprotonation of most substituted arenes, they are routinely used with aromatic substrates that anionically rearrange or cyclize under thermodynamic conditions (Section 1.1.6), in D*o*M reactions with *in situ* electrophilic trapping (Section 1.4) and in the metalation of the more acidic π-deficient heteroaromatics (Section 1.3). In recent years, new bases have been developed that overcome some drawbacks of the traditional D*o*M and namely a) the incompatibility of bromo- and iodoarenes with alkyllithiums and lithium amides which trigger undesired metal-halogen exchange or dehydroelimination reactions, b) the high tendency of certain DMGs (*e.g.*, CN,[47] COOR,[48] $OP(O)(NeM_2)_2$)[49] to undergo nucleophilic attack by the base, self-condensation or anionic *ortho*-Fries rearrangement; c) the requirement for low temperatures (typically –78 °C). Fifty years after the pioneering work of Wittig, who introduced the first magnesiate, Ph_3MgLi,[50] several mixed lithium metal "ate" compounds are now undergoing a deep structural scrutiny and their optimization for use in D*o*M reactions has began to yield surprising but welcome results.[51] Uchiyama and Kondo have introduced the aluminum ate base $^{i}Bu_3Al(TMP)Li$[52] and the TMP-zincate TMP-$Zn^{t}Bu_2Li$[53] for the metalation of base-sensitive arenes (Scheme 1.10), while Queguiner has applied the magnesiates Bu_3MgLi and $Bu_x(TMP)_yMgLi_z$ to the metalation of heteroaryl substrates (Schemes 1.43 and 1.69).[54] While TMP-zincate has given excellent yields in the *ortho*-metalation of benzonitrile and unhindered benzoates, it has proven to be incompatible with haloarenes (**1.54** → **1.55**, Scheme 1.10).

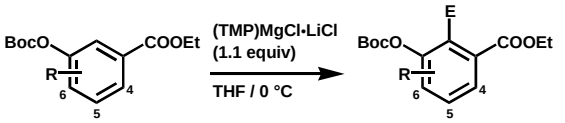


Scheme 1.10

A comparative React-IR study for the metalation of *N*,*N*-diisopropylbenzamide with TMP-zincate and with mesyllithium has revealed two different absorption C=O bands, which, together with ^{13}C NMR, support the hypothesis of an arylzincate intermediate such as **1.57b**. Although the *ortho*-zincation mechanism is considered a more complex process than the conventional *ortho*-lithiation, it is still thought to activate the *ortho*-proton through a CIPE. On the other hand, ^{i}Bu$_3$Al(TMP)Li has been shown to tolerate halogen substituents and to be effective with electron- poor and rich substrates (**1.54** → **1.56**, Scheme 1.10). The stability of the aryllithium metal ate intermediates **1.57a-c** is the key to the wide applicability of these bases even at rt, but at the same time, is a factor that limits the electrophilic quench to the highly reactive I_2 and few benzaldehydes.

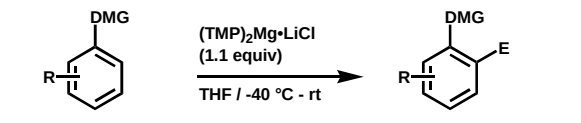
Following the groundbreaking work of Eaton[55] on the poorly soluble magnesium bases R_2NMgCl and poorly effective R_2NMgR' and $(R_2N)_2Mg$, Knochel reported the use of the corresponding mixed Mg/Li amides TMPMgCl•LiCl[56] and $(TMP)_2Mg$•2LiCl[57] which display excellent solubility in THF (0.6 M and 1.2 M, respectively) and improved kinetic basicity. TMPMgCl•LiCl was found to display high FG tolerance (including the PhCO group) but, due to the moderate directing power of the COOEt group, was applied mainly to π-deficient heteroaryl substrates[56a] and electroh-poor benzenes bearing halogens or the

strong and well tolerated OC(O)O^{t}Bu DMG (Scheme 1.11).[56b] Although these electronic features are not required when the more basic $(TMP)_2Mg•2LiCl$ is used, its application in the metalation of electron-rich benzenes has not been fully demonstrated (Scheme 1.12).`[58] Compared to the metal ate complexes, the use of Knochel's mixed Mg/Li bases allows a wider selection of suitable electrophiles through direct quench or through transmetalation of the arylmagnesiated intermediate with CuCN•2LiCl or $ZnCl_2$/CuCN•2LiCl.[56-58] Althought these methodologies are still in their initial phase of development, they have been shown to adequately complement the D*o*M reaction where FG integrity is at risk. Further improvements, especially in the cross coupling of the aryl metal intermediates, can be expected to pave the road to their widespread adoption in the functionalization of aromatic and heteroaromatic substrates.



[a] Obtained by transmetalation with CuCN•2LiCl (0.2 mol%);

Scheme 1.11



[a] Obtained by transmetalation with CuCN•2LiCl (0.2 mol%);
[b] Obtained by Pd-catalyzed cross coupling after metalation with $ZnCl_2$

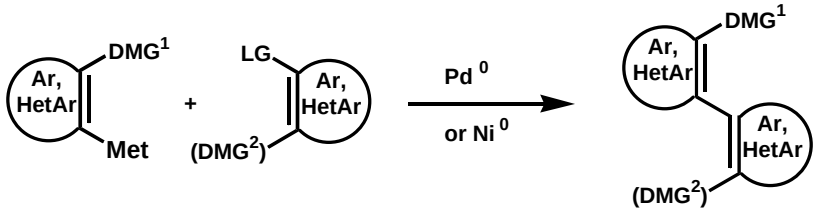
Scheme 1.12

1.1.4 The D*o*M-Cross Coupling Nexus

In the last three decades, virtually all areas of synthetic chemistry have gained a new unexpected breath from the discovery of a number of transition metal-catalyzed methodologies to create aryl-aryl bonds.[59] More recently, these reliable methods have provided the D*o*M reaction with a new *raison d'être* as the metallorganic coupling

partners can be easily obtained from aryl and heteroaryllithium species through Li-metal exchange (Table 1.2).[60] Functionalized aryl chlorides bromides, iodides, triflates can also be obtained by D*o*M tactics. Thus, this fortunate connection allows straightforward access to 1,1'-bis *ortho*-substituted biaryls **1.64** with high synthetic potential as substrates for further D*o*M and, for some of them, further DreM (Directed remote Metalation) and other cyclization reactions. Due to their stability and structural diversity, boronic acids have remarkably strengthened this link as they are extensively coupled by the fine chemical industry for the synthesis of comprehensive and diverse libraries of biaryls and heterobiaryls.[61]

Table 1.2 The D*o*M-Cross Coupling Nexus

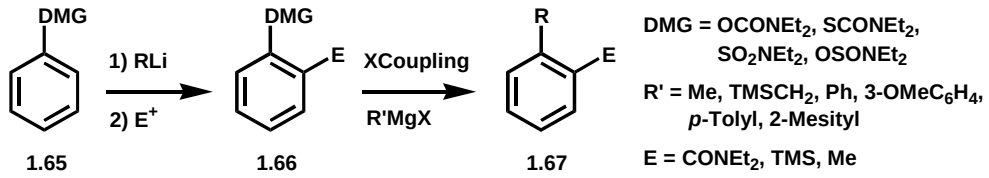


1.62 **1.63** **1.64**

Met	LG	Cat	Xcoupl
$B(OR)_2$	I > Br > OTf	Pd	Suzuki[60a]
MgX	Hal, OTf	Ni	Kumada-Corriu-Tamao[60a]
ZnX	Hal, OTf	Ni	Negishi-Migita[60a]
SnR_3	Hal, OTf	Pd	Stille[60a]
$Si(OR)_3$	Hal, OTf	Pd	Hiyama[60b]
$^1/_3$ In	I, Br, OTf	Pd	Pérez Sestelo-Sarandes[§,60c]
Zn^tBu_2Li	(2-BrPy, 2-BrPh)	Pd	Kondo[§,†,53]
$^1/_3$ MgLi	(2-BrPy, 2-ClPy)	Pd	Queguiner[§,†,54]
Al^iBu_3Li	(PhI)	Pd	Uchiyama[§,†,52]

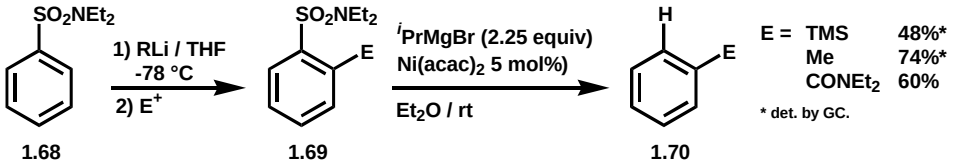
§ Not as yet a named reaction; † Not generalized.

Particularly attractive appears the D*o*M-Kumada nexus that uses the same functionality (*O*-carbamate, *S*-thiocarbamate,[62] tertiary sulfonamides, sulfamates[7o]) both as a DMG and as a leaving group in the coupling reaction, a strategy that offers the option of replacing the DMG with an aryl group when it has served its purpose (Scheme 1.13).



Scheme 1.13

A truly latent DMG is the diethylsulfonamide group which, using the β-hydride donor ability of ^{i}PrMgCl, can be reductively cleaved under Ni-catalysis (Scheme 1.14).



Scheme 1.14

The synthesis of functionalized biaryls through coupling of simple partners has revolutionized the retrosynthetic approach to complex structures. However it is from its marriage to D*o*M that this powerful methodology has acquired a remarkable dowry in high regioselectivity and great resourcefulness. Connubial fruits have largely appeared in medicinal chemistry,[63] material sciences[64] and total synthesis of natural products.[60a,65]

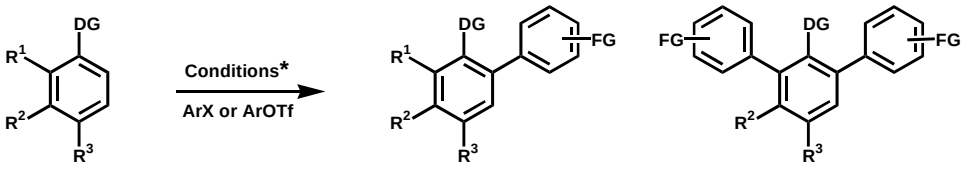
1.1.5 Direct *ortho*-Arylation as an Alternative Methodology to the D*o*M Reaction

In recent years, the synthesis of *ortho*-substituted biaryls and heterobiaryls has been approached through transition metal-catalyzed direct arylation, an emerging methodology

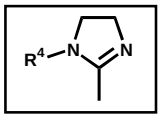
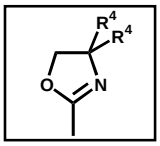
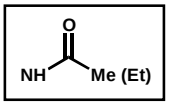
based on the direct coupling of a non-activated aryl C-H bond with an activated arene (an aryl halide or pseudohalide).[66] π-Electron-rich substrates have been an ideal workbench for these studies because the formation of the initial palladate or rhodium equivalent is facilitated by the highly nucleophilic character of these heteroarenes. However, the attenuated nucleophilicty of simple arenes requires a Lewis-basic directing group capable of promoting this step by bringing the metal into close proximity of the *ortho*-position, much like it has been postulated to do with a base in the mechanism of D*o*M. Heterocyclic rings like pyridines,[66,67] quinolines, pyrazoles, triazoles,[68] imidazolines,[69] oxazolines,[67-,70] benzoxazoles[71] have proved to fulfil this role quite well. The use of functional groups as directing groups (DGs) for this process has also begun to reveal the synthetic potential of direct arylation for complementing or, in some cases, successfully competing with the D*o*M reaction (Table 1.3). Thus, for instance, acetyl and propionyl anilides (entries 14-16) can be *ortho*-arylated with aryl iodides without separately preparing their corresponding *ortho*-arylmetalloid coupling partner.[72] The efficient *ortho*-arylation of benzoic acids (entry 22-27),[73] benzaldehydes (entries 28-29)[74] and phenols (entries 7-9)[75] constitutes an attractive alternative to the D*o*M-cross coupling link of these substrates since it allows to circumvent their otherwise obligatory conversion to oxazolines,[76] α-aminoalkoxides[77] and OMOM[78] derivatives, respectively. Some of the DGs so far used in direct arylation are similar to common DMGs and thus the possibility to exploit a D*o*M-direct arylation nexus may be envisaged. For example, the D*o*M of oxazolines (entries 3-6), (het)aromatic aldehydes, secondary amides (entry 14-16)[79] is well established, and this opportunity exists in principle for the weak OH[80] and COOH DMGs. On the contrary, enolizible ketimines (entries 10-12)[67,81] and *N*-acylated

imidazolines (entry 2) have not been subjected to D*o*M, and both aldimines (entry 13) and *N*-unsubstituted imidazoline (entry 1), which have some directing abilities in D*o*M,[82] suffer extensive diarylation.

Table 1.3 Directed C-H Arylation of Aromatic Hydrocarbons

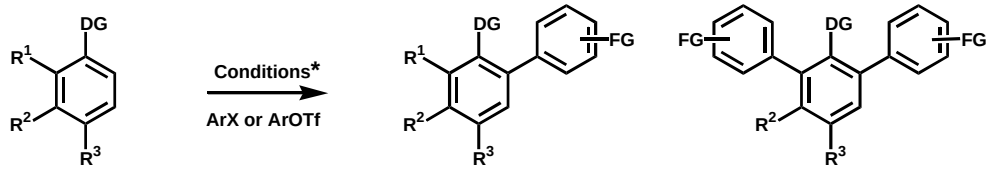


1.71 1.72 1.73

Entry	R^4	DG	R^1	R^2	R^3	1.72:1.73	FG	Yld(%)	Ref.
1	H					0:100	H	90	69
2	COR					~ 80:20	H	76-88	69
3	H		Me			99:1	H, 4-COOR, 4-Me, 4-Ac, 4-OMe, 2-OMe, 4-CN, 3-COOMe, 3,5-di-CF_3, 2-Cl, 2-Me, 4-$CH=CH_2$, 3-CF_3, 3-PhCO, 3-COOEt	51-99	67, 68, 70
4	H			Me, CF_3		85:15 - 99:1	H	73-91	69
5	H					25:75 or 0:100 (XS of PhBr)	H	60-99	69
6	Me					99:1	H	11	69
7		OH	^{t}Bu, Me, Et. OMe, Ph, ^{i}Pr			99:1	H, 4-Ac, OMe, 4-NMe_2, 4-CH=CH2, 2,6-diMe_2, 2,3-$(CH=CH)_2$,	76-96	75a-c
8				Me, OMe, ^{t}Bu		38:62 - 99:1	4-OMe	39-51	75a
9						1:99	H, 4-OMe, 2,4,6-tri-Me	18-69	75a, 75d
10	Me, Et	CR^4=NAr				80:20 - 99:1	H, 4-Ac, 4-COOEt, 4-OMe	56-91	67, 81a
11	Me			Me, CF_3, 2,3-$(CH=CH)_2$		99:1	H, 4-F, 4-Me, 4-OMe	74-95	81b
12	Me				H, Me, OMe	99:1	4-CF_3, 4-Ac, 2-Me, 4-OMe 4-COOEt, 3-COOEt,	56-79	81a
13	H					1:99	H	92	81b
14					Me	1:99 - 99:1	4-I, 4-Me, 3-OCF_3	34-79	72
15			OMe			99:1	3,5-di-Me, 4-Br	82-90	72
16				Br		99:1	4-^{t}Bu, 3-Cl	82-91	72

*** Entries 1-2: 2.5 mol% $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, 10 mol% PPh_3 / NMP / 120 °C / 20 h; entry 3-6: as in entries 1-2 or 2.5 mol% $[\{RuCl_2(p\text{-cymene})\}_2]$, 10 mol% $R_2P(O)H$ NMP / 120 °C / 23h or 2.5 mol% $[\{RuCl_2(p\text{-cymene})\}_2]$ / 30 mol% $MesCO_2H$ / PhMe / K_2CO_3 / 120 °C or 5.0 mol% $[RuCl_3(H_2O)_n]$ / K_2CO_3 / NMP / 120 °C / 22h; entries 7-9: 5 mol% $[RhCl(PPh_3)_3]$ / 15 mol% $PR_2(OAr)$ / Cs_2CO_3 or 10 mol% $[\{RhCl(COD)\}_2]$ / 30 mol% $P(NMe_2)_3$ / PhMe, reflux / 18h; entries 10-13: 2.5 mol% $[\{RuCl_2(p\text{-cymene})\}_2]$, 10 mol% $R_2P(O)H$ NMP / 120 °C / 23h or 5.0 mol% $[RuCl_3(H_2O)_n]$ / K_2CO_3 / NMP / 120 °C / 22h as in entries 1-2; entries 14-16: 5 mol% $Pd(OAc)_2$ / AgOAc / TFA / 130 °C / 0.5 - 5h.**

Table 1.3 Directed C-H Arylation of Aromatic Hydrocarbons (Cont'd)



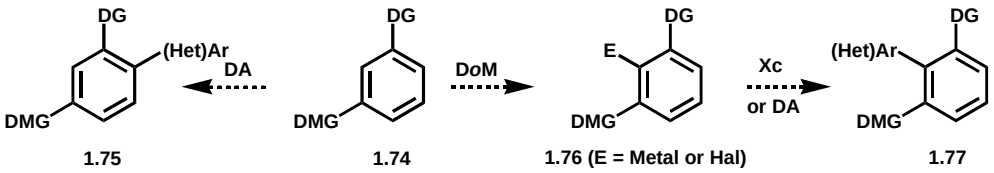
1.71 1.72 1.73

Entry	R^4	DG	R^1	R^2	R^3	1.72:1.73	FG	Yld(%)	Ref.
17		$CONH^iPr$				1:99	3-OCF_3	73	83
18				H, Me	Me	99:1	4-^{t}Bu, 4-Ac, 3-OCF_3	54-96	83
19				Br		99:1	p-Cl, 4-OCF_3	79-84	83
20			Cl			99:1	4-Br	59	83
21			$(CH=CH)_2$			99:1	3-CF_3, 4-COOEt	58-61	83
22		COOH				1:99	H, 4-CF_3	71-82	73
23				Me, ^{i}PrO, Br, N_2O, CF_3, COOMe, Ph		99:1	H, 3,5-di-CF_3, 3-F, 4-Me, 4-Cl, 3,5-di-Cl	53-83	73
24			$(CH=CH)_2$			99:1	3-Me, 4-^{i}Pr, 3,5-di-Me	54-67	73
			Me, OMe	Me, OMe					
25					Me, COOMe	1:99	4-CF_3	75-79	73
26				F		1:99	4-CF_3, 4-Me	67-91	73
27			Me, Ph			99:1	3-Me, 4-CF_3, 3,5-di-Me	67-91	73
28		CHO			CHO, NMe_2, ^{t}Bu, OMe	99:1	4-OMe, 4-Ac, 4-Me	56-92	74
29						1:99	H	85	74

* Entries 17-21: 5 mol% $Pd(OAc)_2$ / AgOAc / TFA / 130 °C / 0.5 - 5h. Entries 22-27: 5 mol% $Pd(OAc)_2$ / AgOAc / AcOH / 4.5-7h or 5 mol% $Pd(Ac)_2$ / 10 mol% $PAd_2{}^nBu$ / Cs_2CO_3 / MS 3 A / DMF / 145 °C / 24 h; entries 28-29: 1 mol% $Pd(OAc)_2$ / 2 mol% NHC Ligand / Cs_2CO_3 / dioxane / 80 °C.

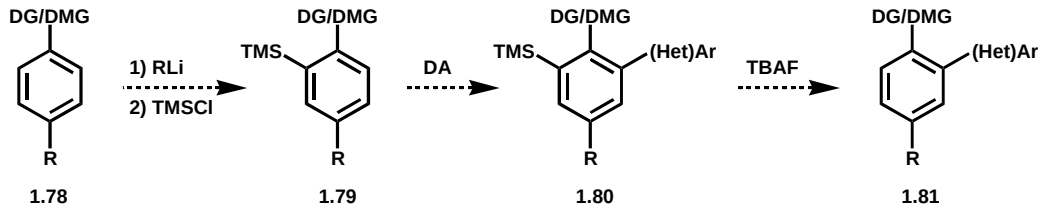
Similarly, pivalanilides which, unlike acetyl and propionyl anilides (entries 14-16), are suitable directing groups for both direct arylation[83] and for D*o*M,[84] are extremely difficult to hydrolyze when *ortho*-arylated. On the other hand, the acid-labile NHBoc group, which is typically preferred to anilides, has not been tested for stability under the conditions required by the direct arylation. Besides its inherently shorter approach to *ortho*-substituted biaryls and heterobiaryls, the direct arylation displays a high FG compatibility that includes halogens, esters and nitro groups; furthermore, the heightened

interest of the scientific community for this efficient approach is permitting the rapid development of catalysts and conditions capable of arylating unactivated arenes with inexpensive aryl chlorides[68,73-75a,b] and, in the case of acetanilides, with aryl boronic acids (direct Suzuki reaction),[85] aryltrialkoxysilanes (direct Hiyama reaction) [86] and even with unactivated arenes (dual C-H activation).[87] The most relevant drawback of this reaction is the bis-*ortho*-arylation which occurs in all unsubstituted DG-bearing benzenes (entry 6 is the only exception, 11%). Indeed, a glance at Table 1.3 shows that most substrates which do not undergo bis-arylation are *ortho*- and *meta*-substituted, whereas very few are *para*-subtituted (entries 12 and 28). In general, the direct arylation is sensitive to hindrance in the vicinity of the DG, and a *meta*-methyl group is often sufficient to direct the arylation solely towards the unhindered *ortho*-position (entries 11, 16, 23 and 26). This behaviour, also observed with many other *meta*-substituents (including DMGs like OMe, CF_3, COOMe, Br and F), complements well the general course of the D*o*M reaction in which the position between two DMGs undergoes selective deprotonation (Scheme 1.15).



Scheme 1.15

Thus, far from appearing redundant, the development of D*o*M-compatible DGs should be viewed as an opportunity to strengthen both methodologies. Furthermore, the difficult mono-arylation of 4-substituted and unsubstituted substrates may benefit from silicon *ortho*-protection introduced by D*o*M (Scheme 1.16).

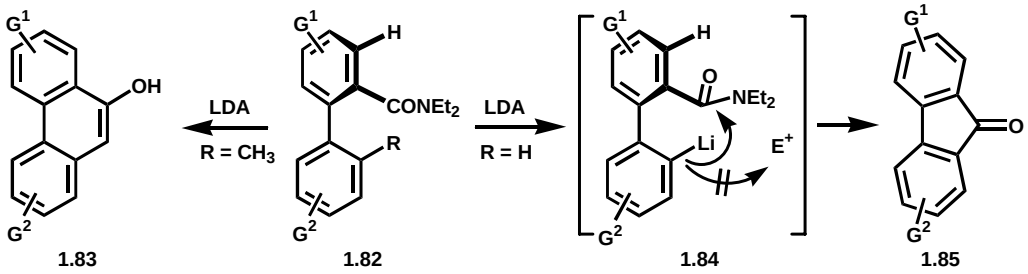


Scheme 1.16

As the potential of this emerging methodology is rapidly unveiled, the growing interest catalyzed by these results is expected to lead to a rapid optimization of these protocols with an increasing number of versatile functional groups. Until then, the D*o*M reaction will reliably provide valuable precursors for the well established, soon *classic* transition metal-catalyzed cross coupling route.

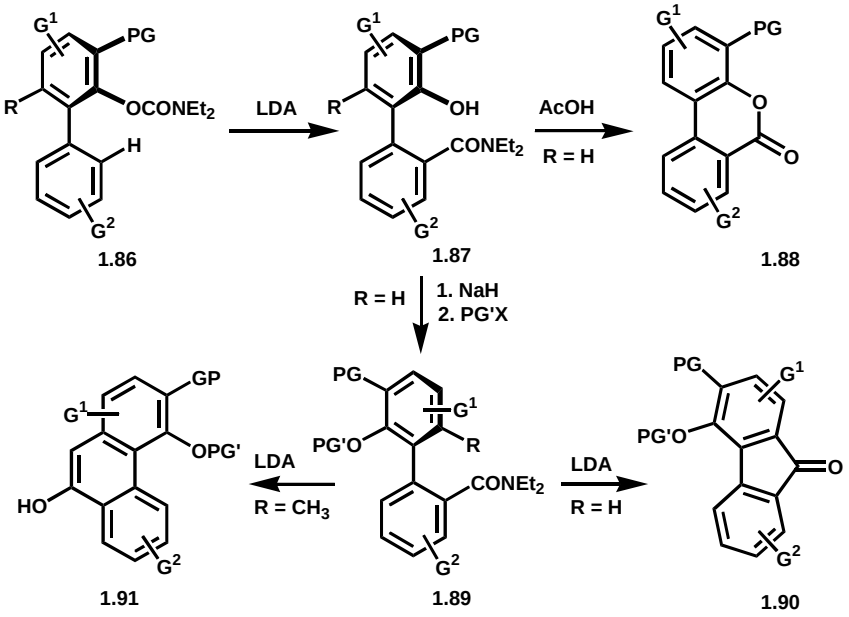
1.1.6. The D*o*M-DreM Connection

Some fifteen years ago, research in the Snieckus group showed that a DMG may reach far beyond the *ortho* hydrogen atoms. In accordance with and significant support of the hypothesis of a CIPE, some DMGs ($CONEt_2$,[88] $OCONEt_2$,[89] COOH[90]) placed on biaryls were found to facilitate the abstraction of aromatic hydrogens on remote positions on the alternate ring. In the Directed remote Metalation (DreM) of the amide **1.82**, in spite of the availability of hydrogen atoms *ortho* to the DMG, treatment with LDA leads to deprotonation of the alternate ring to generate the lithiated species **1.84**, which is too-short lived to be trapped by an external electrophile and undergoes reaction intramolecularly with the amide group, leading to fluorenone **1.85** (Scheme 1.17). This methodology has found rational extension in its tolyl-DreM equivalent, which constitutes a general regioselective route to 9-phenanthrols (**1.82** → **1.83**).[91]



Scheme 1.17

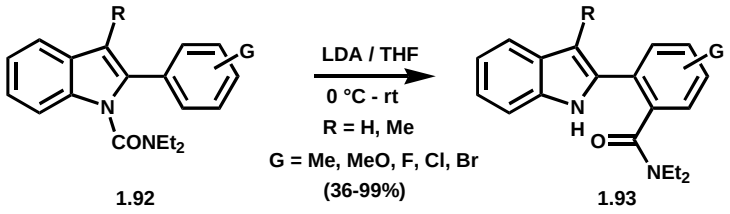
Biaryl *O*-carbamates **1.86** show a similar behaviour (Scheme 1.18) provided the *ortho* position to the DMG is substituted or protected (usually with $SiEt_3$) to prevent anionic *ortho* Fries rearrangement.



Scheme 1.18

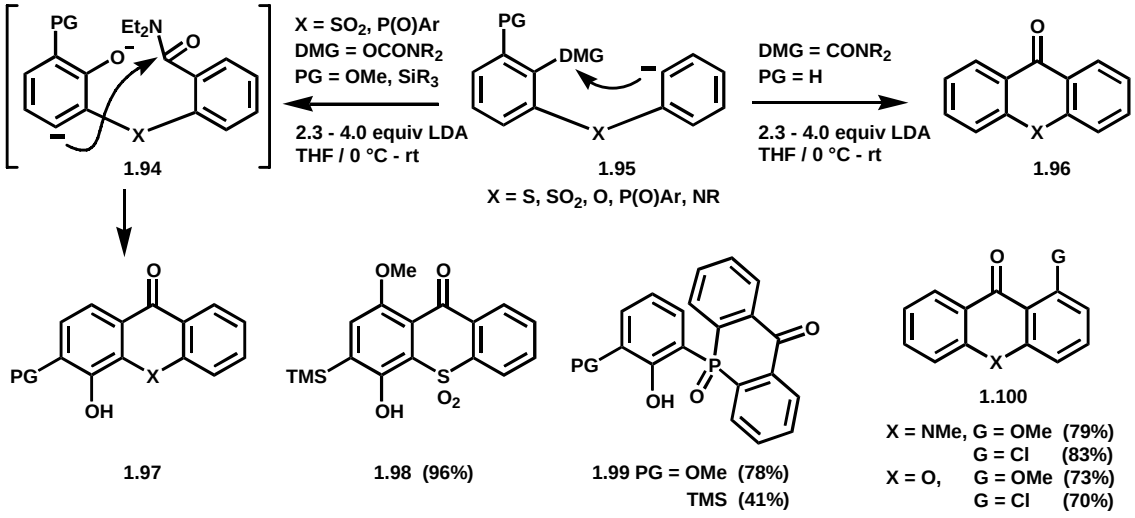
In this case, the migration of the carbamoyl group, describable as an anionic remote Fries rearrangement, yields hydroxyphenyl benzamides **1.87** which, upon acid-catalyzed cyclization, is converted to the useful dibenzo[*b*,*d*]pyran-6-one framework **1.88**. Alternatively, OH-protected arylbenzamide **1.89** may be subjected to a second DreM and

converted to a fluorenone **1.90**. The sequential combination of biaryl *O*-carbamate migration and vinylogous tolyl amide cyclization (**1.86→1.87→1.89→1.91**) has also been applied to the total synthesis of natural products.[92] A potentially useful and general variation of the carbamoyl migration has been recently demonstrated in the reaction of *N*-carbamoyl-2-aryl (and -2-heteroaryl) indoles **1.92** to **1.93** using LDA (Scheme 1.19).[93]



Scheme 1.19

Far from being limited to biaryls, the DreM reaction was proven feasible in systems where an atom or a group (S, SO_2, O, P(O)Ar, NR) separates the two aromatic rings (Scheme 1.20).



Scheme 1.20

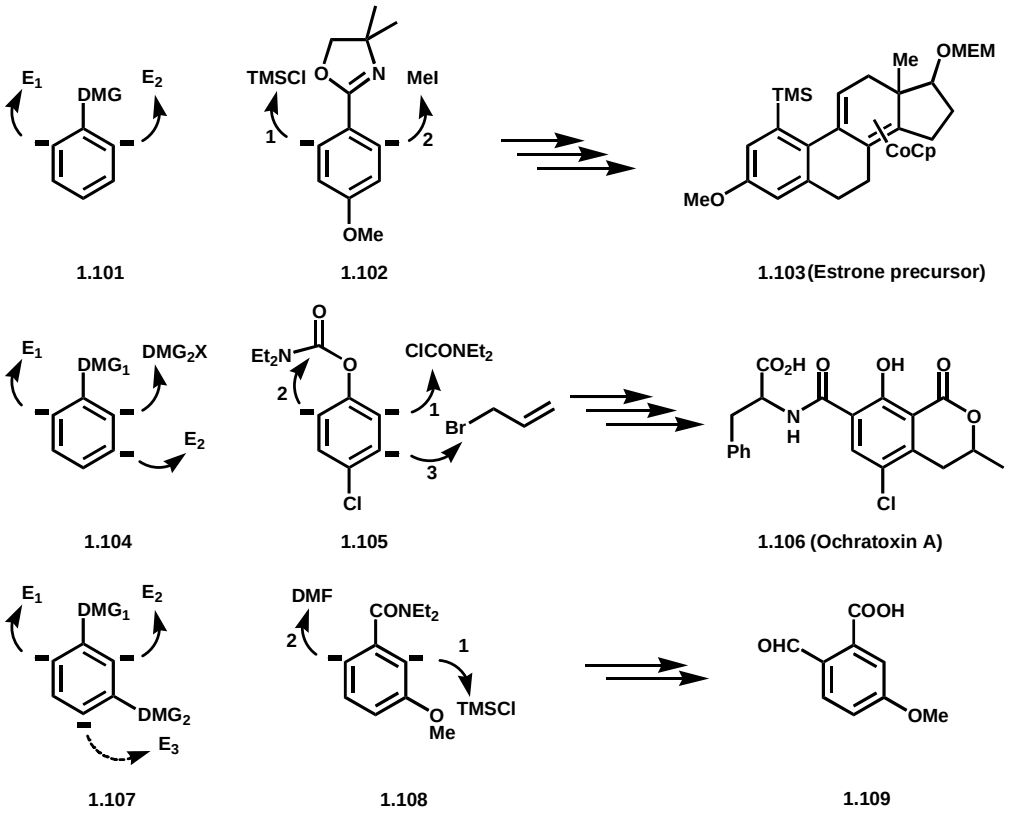
This extension opens an unprecedented route to xanthones,[94] thioxanthones,[95] acridones[96] and dibenzophopshorinones[97] whose degree of functionalization mirrors the complexity of the coupling partners from which biaryls can be conveniently derived. The derived products **1.98-1.100** illustrate the efficiency of the DreM reactions.[98,11] Other useful extensions of this methodology will be discussed in Chapters 2 and 3.

1.1.7. Applications of the D*o*M Reaction

The combination of electrophilic aromatic substitution (EAS),[99] nucleophilic aromatic substitution (S_NAr),[100] vicarious nucleophilic substitution (VNS)[101] and other minor or emerging methodologies provides the chemist with a well equipped synthetic toolbox for the functionalization of the aromatic ring.

Nevertheless, it was with the development of the D*o*M strategy that high selectivity, wide scope and considerable versatility were attained for the field of synthetic aromatic and heteroaromatic chemistry. However, this methodology cannot be seen as an "all-in-one" technology capable of matching the full potential of the other methods. For instance, the D*o*M process is not compatible with some of the groups (NO_2, COR, SO_2Me, SOMe) which efficiently activate aromatic substrates for VNS and S_NAr processes.[102] Similar conclusions apply to a comparison with EAS whose potential in nitration and sulfonation reactions or compatibility with substituents such as Br, I and NO_2 have no parallel in D*o*M. Nevertheless, however instinctive its use has become, the EAS suffers, in reality, from harsh conditions and formation of regioisomeric mixtures which invariably impose a separation step. Through high selectivity, on the contrary, the D*o*M methodology provides shortcuts to substitution patterns otherwise accessible only through very prolonged sequences. Thus, contiguously substituted systems (1,2-, 1,2,3-, 1,2,3,4-,

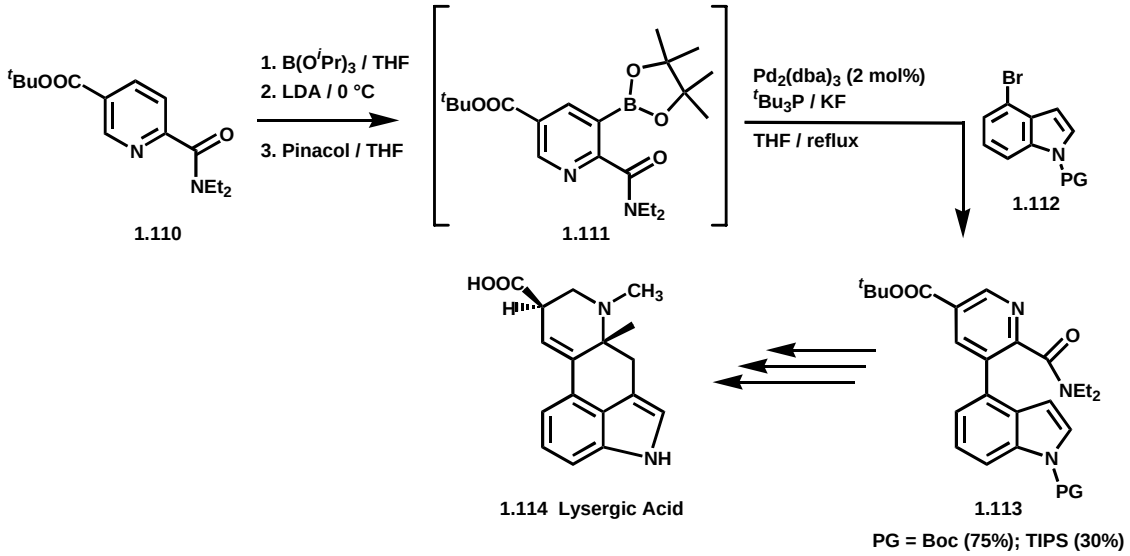
1,2,4,5-) appear within reach by the DoM strategy (Scheme 1.21).[103] The use of one or two DMGs of different power allows the rapid construction of tri- and tetrasubstituted systems. In theory even pentasubstituted benzenes may be obtained from 1,3-$(DMG)_2$ systems such as **1.107** provided the substituents progressively installed are (or are made) compatible with strong bases.



Scheme 1.21

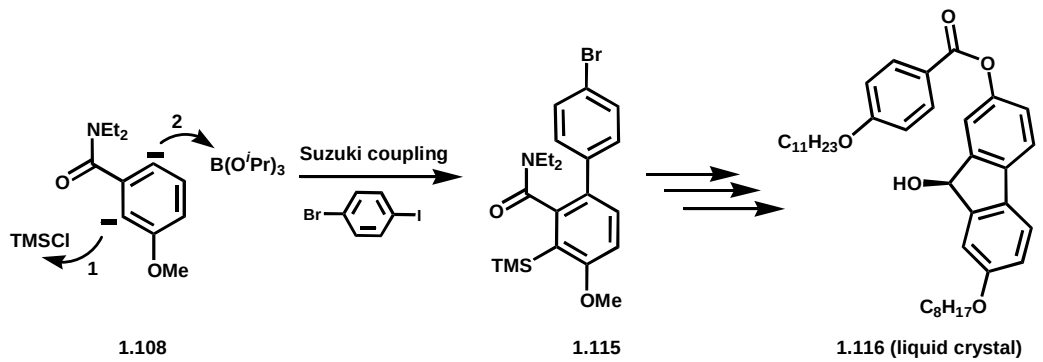
In other cases (ring-walking method), a second DMG may be installed through D*o*M (**1.105**, step 1) or by *ortho*-Fries rearrangement of an aryl carbamate (**1.105**, step 2). Finally, the provisional exploitation of hindrance factors (**1.107**, large DMG_1 or/and DMG_2) or silicon protection (**1.108**, E_2 = TMSCl**)**, may furnish 1,2,4- and 1,2,4,5-substituted systems. The potential of D*o*M, as amplified by the versatile lithium species, has been largely exploited in the total synthesis of natural products.[104] In the case of

lysergic acid, for instance, the construction of the main frame was approached by a sequence of D*o*M-boronation and *in situ* cross coupling that furnished the key intermediate **1.113** in good yield (Scheme 1.22).[105]



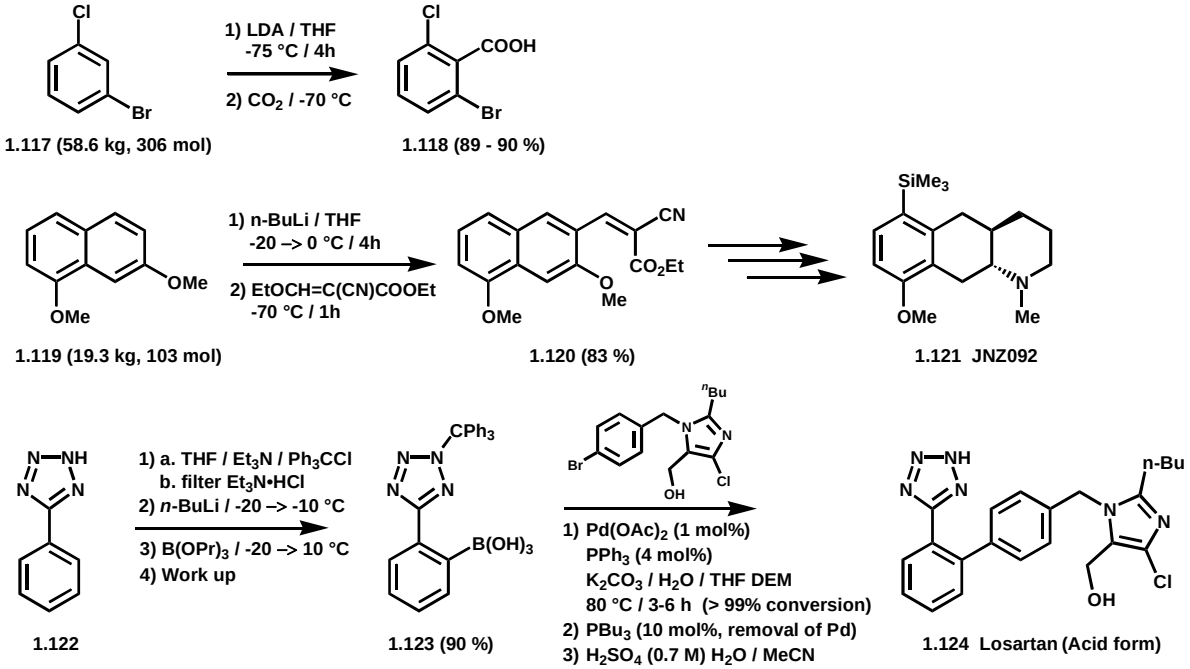
Scheme 1.22

Applications of key D*o*M steps connected to Suzuki-Miyaura coupling methodology and DreM have also led to new molecules displaying liquid crystalline properties (Scheme 1.23).[106] In the past decade the DoM reaction has enjoyed increasing application in large-scale process chemistry for the preparation of required amounts for advanced drug discovery studies and commercial drugs. To illustrate, careful optimization of the experimental conditions in the metalation of 3-chloro bromobenzene (**1.117**) by Merck chemists led to the synthesis of 2-bromo-6-chlorobenzoic acid **1.118** on a 60 kg scale and in excellent yields (89-90%, Scheme 1.24).[3c] Similarly, at Novartis, a pilot plant synthesis of the lead compound JNZ092 was devised that involves the metalation of the dimethoxynaphthalene **1.119** and electrophile quench to give **1.120** in 83% yield.[3d]



Scheme 1.23

Finally, in the synthesis of Losartan **1.124** (ca. 1000 Kg/year), Merck and Dupont, now BMS, chemists used the tetrazole moiety as a DMG to efficiently install a boronic group (**1.122→1.23**).[3e]



Scheme 1.24

These examples demonstrate that the D*o*M reaction has not only a recognized potential in the modification of a DMG's *ortho*-environment but, through its privileged connections

with rapidly growing methods (metal-catalyzed cross coupling, RCM, DreM, direct arylation) imposes the choice and exploration of new synthetic routes. The didactic relevance of the D*o*M reaction has also been recently recognized with a dedicated section in the best-seller "Strategic Applications of Named Reactions in Organic Synthesis".[107]

1.2. References

[1] Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* **1939**, *61*, 109-112.

[2] Wittig, G.; Pockels, U.; Droge, H *Chem. Ber.* **1938**, *71B*, 1903-1912.

[3] a) Payack, J. F.; Vazquez, E.; Matty, L.; Kress, M. H.; McNamara, J. *J. Org. Chem.* **2005**, *70*, 175-178. b) Keen, S. P.; Cowden, C. J.; Bishop, B. C.; Brands, K. M. J.; Davies, A. J.; Dolling, U. H.; Lieberman, D. R.; Stewart, G. W. *J. Org. Chem.* **2005**, *70*, 1771-1779. c) Hickey, M. R.; Allwein, S. P.; Nelson, T. D.; Kress, M. H.; Sudah, O. S.; Moment, A. J.; Rodgers, S. D.; Kaba, M.; Fernandez, P. *Org. Process Res. Dev.* **2005**, *9*, 764-767. d) Bänziger, M.; Küsters, E.; La Vecchia, L.; Marterer, W.; Nozulak, J. *Org. Process Res. Dev.* **2003**, *7*, 904-912. e) Miyaura, N. in *Science of Synthesis,* Kaufmann, D.; Ed.; Thieme, Stuttgart, 2004, Vol. 6, p. 292. Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D.M.; Verhoeven, T.R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 6391-6394.

[4] a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306-312. b) Gschwend, H. W.; Rodriguez, H. R., Eds. *Org. React.* New, York, **1979**, *26*, 1-360. c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206-2225. d) Macklin, T. K.; Snieckus, V. in *Handbook of C-H Transformations*, Dyker, G. Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, pp. 106-118.

[5] Langer, A. W. *Adv. Chem. Ser.* **1974**, *No.* 130. However, benzene is quantitatively deprotonated by the combination ^{n}BuLi•TMEDA.

[6] Rohonnstad, P.; Wensbo, D. *Tetrahedron Lett.* **2002**, *43*, 3137-3139. Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J.-L. *J. Chem. Soc. Perkin Trans.* **1995**, 1265-1271. Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* **2002**, *8*, 799-804.

[7] a) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853-856. b) Meyers, A. I.; Mihelich, E. D. *Tetrahedron* **1975**, *40*, 3158-3159. c) Gschwend, H. W.; Hamden, A. *J. Org. Chem.* **1975**, *40*, 2008-2009. d) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823-1824. e) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979-3982. f) Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042-4044. g) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183-1186. h) Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 900-903. i) Watanabe, H.; Schwarz, R. A.; Hauser, C. R.; Lewis, J.; Slocum, D. W. *Can. J. Chem.* **1969**, *47*, 1543-1546. j) Christensen, H. *Synth. Commun.* **1975**, *5*, 65-78. k) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133-1136. l) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798-4801. m) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935-1937. n) Gray, M.; Chapell, B. J.; Felding, J.; Taylor, N. J.; Snieckus, V. *Synlett* **1998**, 422-424. o) Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519-2522. p) Kaush, M.; Hoppe, D. *Synthesis* **2006**, *10*, 1575-1577 and *Synthesis* **2006**, *10*, 1578-1589.

[8] a) For the hydrolysis of the oxazoline DMG see: Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372-1379. b) For the hydrolysis of the OMOM and

NHBoc groups see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Third ed.; John Wiley & Sons, Inc., 2002.

[9] Milburn, R. R.; Snieckus, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 888-891.

[10] Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066-4068.

[11] a) Chauder, B.A.; Kalinin, A.V.; Taylor, N.J.; Snieckus, V. *Angew, Chem., Int. Ed.*, **1999**, *38*, 1435-1438. b) Cai, X.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2293-2295. c) Fu, J.-m.; Zhao, B.-p.; Sharp, M.J.; Snieckus, J. *Can J. Chem.* **1994**, *72*, 227-236. d) James, C.A.; Snieckus, V. *Tetrahedron Lett.* **1997**, *38*, 8149-8152. e) Mohri, S.-i.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072-7073.

[12] a) Spletstoser, J.T.; White, J.M.; Tunnori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* **2007**, *129*, 3408-3419. b) White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* **2000**, *122*, 11995-11996. c) Zhao, Y.; Snieckus, V. Manuscript in preparation. d) Morin, J. A.; Snieckus, V. Manuscript in preparation.

[13] Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875-9883.

[14] Charette, A. B.; Chua, P. *Synlett* **1998**, 163-165.

[15] Comins, D. L. *Synlett* **1992**, 615-625 and references therein. Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1989**, *54*, 3730-3732.

[16] a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389-5393. Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1993**, *32*, 568-570. Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10-11. Richards, C. J.; Damalidis, T.; Hibbs, D. E.; M.B., H. *Synlett* **1995**, 74-76. Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79-81. Aubé, J.; Heppert, J. A.; Milligan, M. L.; Smith, M. J.; Zenk, P. *J. Org. Chem.* **1992**, *57*, 3563-3570 (chromium complex). Han, J. W.; Son, S. U.; Chung, Y. K. *J. Org. Chem.* **1997**, *62*, 8264-8267.

[17] Price, D.; Simpkins, N. S. *Tetrahedron Lett.* **1995**, *36*, 6135-6136. Quattropani, A.; Bernardinelli, G.; Künding, E. P. *Helv. Chim. Acta* **1999**, *82*, 90-104.

[18] Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685-686.

[19] Metallinos, C.; Snieckus, V. *Org. Lett.* **2002**, *4*, 1935-1938.

[20] Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899-2902.

[21] Koide, H.; Uemura, M. *Chirality* **2000**, *12*, 352-359.

[22] Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1985**, *19*, 356-363.

[23] Klumpp, G. *Recl. Trav. Chim. Pays-Bas* **1986**, 105, 1-21.

[24] Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092-7093. Luitjes, H.; de Kanter, F. J. J.; Schakel, M.; Schmitz, R. F.; Klumpp, G. W. *J. Am. Chem. Soc.* **1995**, *117*, 4179-4180. Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919-4927.

[25] Hay, D. R.; Song, Z.; Sminth, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145-8153.

[26] Bauer, W.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1989**, *111*, 7191-7198.

[27] McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805-1810. McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *J. Am. Chem. Soc.* **1985**, *107*, 1810-1815.

[28] Review: Wheatley, A.E.H. *Eur. J. Inorg. Chem.* **2003**, 18, *3291-3303*. Linnert, M.; Bruhn, C.; Rüffer, T.; Schimdt, H.; Steinborn, D. *Organometallics* **2004**, *23*, 3668-3673. Clayden, J.; Davies, R. P.; Hendy, M. A.; Wheatley, A. E. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1238-1240. Jastrzebski, T. B. H.; van Koten, G.; Konijn, M.; C.H., S. *J. Am. Chem. Soc.* **1982**, *104*, 5490-5492. Harder, S.; Boersma, J.; Brandsma, L.; Van Heteren, A.; Kanters, J. A.; Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 7802-7806. Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J. A. *J. Organomet. Chem.* **1988**, *339*, 7-15.

[29] Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628-10636.

[30] a) Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259-2268. b) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640-8647. c) Roger, A.; Maliakal, A. J.; Collumn, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421-422.

[31] Hosmane, N. S.; Yang, J.; Zhang, H.; Maguire, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 5150-5151. Eaborn, C.; Lu, Z.-R.; Hitchcock, P. B.; Smith, J. D. *Organometallics* **1996**, *15*, 1651-1655.

[32] a) Riggs, J. C.; Singh, K. J.; Yun, M.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 13709-13717. b) Singh, K. J.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 13753-13760. Collum has also coauthored an analogous study on the D*o*M of aryl oxazolines: Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259-2268.

[33] A DFT study on the TS leading to **1.39d**, does not involve the coordination of fluorine, suggesting that the cooperative assistance of this group is due only to inductive effects.

[34] van Eikema Hommes, N. J. R.; von Ragué Schleyer, P. *Tetrahedron* **1994**, *50*, 5903-5916.

[35] Shirley, D. A.; Johnson, J. R.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *209-216*.

[36] Gilman, H.; Soddy, T. *J. Org. Chem.* **1957**, *22*, 1716-1717.

[37] Schlosser, M. *Angew. Chem. Int. Ed.* **1998**, *110*, 1496-1513.

[38] Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 6551-6554. Rausis, T.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 3351-3358.

[39] Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett* **1990**, 747-748.

[40] Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376-393.

[41] Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731-732. The far reaching effects of fluorine are noteworthy: while uncomplexed ^{n}BuLi forms the unreactive

complex **1.17** with anisole (Scheme 1.4), fluoroanisoles **1.34** and **1.35** (Scheme 1.6) are deprotonated under the same conditions.

[42] Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430-5434.

[43] Nguyen, T.-H.; Chau, N.T.T.; Castanet, A.-S.; Nguyen, K.P.P.; Mortier, J. *J. Org. Chem.* **2007**, *72*, 3419-3429.

[44] Shimano, M.; Meyers, A.I. *J. Am. Chem. Soc.* **1994**, *116*, 10815-10816.

[45] van Eikema Hommes, N. J. R.; von Ragué Schleyer, P. *Angew. Chem. Int. Ed.* **1992**, *31*, 755-758.

[46] Wakefield, B. J. *The Chemistry of Organolithium Compounds*, Pergamon, Oxford, 1974.

[47] Ahlbrecht, H.; Düber, E.-O. *Synthesis* **1982**, 273-275.

[48] Upton, C.J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094-1098.

[49] Watanabe, M.; Date, M.; Kawanishi, K.; Tsukazaki, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 2564-2566.

[50] Wittig, G.; Meyer, F. J.; Lange, G. *Justus Liebigs Ann, Chem.* **1951**, *571*, 167-201. Wittig, G. *Angew. Chem.* **1958**, *70*, 65-71.

[51] For a review see: Mulvey, R.E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed*. **2007**, *46*, 3802-3824.

[52] 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. Uchiyama, M.; Naka, H.; Matsumoto, Y.; Ohwada, T. *J. Am. Chem. Soc.* **2004**, *126*, 10526-10527.

[53] Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539-3540.

[54] a) Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron Lett.* **2004**, *45*, 6697-6701. b) Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G; Marsais, F. *Tetrahedron Lett.* **2004**, *45*, 7873-7877.

[55] Eaton, P. .E.; Lee, C.-H.; Xion, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016-.8018. Eaton, P. E.; Lukin, K. A. *J. Am. Chem. Soc.* **1993**, *115*, 11370- 11375. Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576-4578.

[56] a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958-2961. b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673-5676.

[57] Clososki, G.; Rohbogner, C.J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684. Rohbogner, C.J.; Clososki, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1503-1507.

[58] For the application of this base to the metalation of aryl $OP(O)(NMe_2)_2$ see Schemes 3.12-3.14.

[59] Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.; de Mejere, A.; Diederich, F. Eds.; Wiley-VCH: Weinheim, Germany, 2004: Vol. 2, pp 761-813.

[60] a) For a detailed discussion of this nexus, see Anctil, E.; Snieckus, V. in ref. 59. b) Seganish, W.M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 6790-6795. c) Pena, M.A.; Pérez Sestelo, J.; Sarandeses, L.A. *J. Org. Chem.* **2007**, *72*, 1271-1275.

[61] Baxendale, I.R.; Griffiths-Jones, C.M.; Ley, S.V.; Tranmer, G.K. *Chem. Eur. J.* **2006**, *12*, 4407-4416. Collins, I. *J. Chem. Soc., Perkin Trans. 1*, **2002**, *17*, 1921-1940.

[62] Puumala, K.A., M.Sc. Thesis, University of Waterloo, Canada, 1997.

[63] Heald, R.A.; Stevens, M.F.G. *Org. Biol. Chem.* **2003**, *1*, 3377-3389. Peukert, S.; Brendel, J.; Pirard, B.; Bruggemann, A.; Below, P.; Kleemann, H.-W.; Hemmerle, H.; Schmidt, W. *J. Med. Chem.* **2003**, *46*, 486 -498. Wan, Y.; Wallinder, C.; Plouffe, B.; Beaudry, H.; Mahalingam, A. K.; Wu, X.; Johansson, B.; Holm, M.; Botoros, M.; Karlen, A.; Pettersson, A.; Nyberg, F.; Fandriks, L.; Gallo-Payet, N.; Hallberg, A.; Alterman, M. *J. Med. Chem.* **2004**, *47,* 5995-6008.

[64] a) McCubbin, J.A.; Xia, T.; Wang, R.; Zhao, Y.; Snieckus, V.; Lemieux, R.P. *J. Am. Chem. Soc.* **2004**, *126*, 1161-1167. b) McCubbin, J.A.; Xia, T.; Zhao, Y.; Snieckus, V.; Lemieux, R.P. *Chem. Mater.* **2005**, *17*, 2574-2581. c) Laufer, R.; Veith, U.; Taylor, N.J.; Snieckus, V. *Can. J. Chem.* **2006,** *84*, 356-369. d) Müller, H.; Petersen, J.; Strohmaier, R.; Gompf, B.; Eisenmenger, W.; Vollmer, M.S.; Effemberger, F. *Adv. Mater.* **1996**, *8*, 733-737.

[65] Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126-1136. Benesch, L.; Bury, P.; Guillaneux, D.; Houldsworth, S.; Wang, X.; Snieckus, V. *Tetrahedron Lett.*, **1998**, *39*, 961-964. Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguiner, G.; Siddiqui, M.A.; Snieckus, V. *J. Org. Chem.*, **1995**, *60*, 292-296.

[66] Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238.

[67] Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**,*64*, 6115-6124.

[68] Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299-2302.

[69] Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113-3119.

[70] Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem. Int. Ed.* **2006**,*45*, 2619-2622.

[71] Yang, F.; Wu, Y.; Zhu, Z.; Zhang, J.; Li, Y. *Tetrahedron* **2008**, *64*, 6782-6787.

[72] Shabashov, D.; Daugulis, O.; *J. Org. Chem.* **2007**, *72*, 7720-7725.

[73] Chiong, H.A.; Phan, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879-9884.

[74] Gürbüz, N.; Özdemir, I.; Cetinkaya, B. *Tetrahedron Lett.* **2005**, *46*, 2273-2277.

[75] a) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669-8681. b) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112-114. c) Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Lewis-Alleyne, L. C.; Long, P. D.; Polo-Céron, D.; Prashar, S. *Chem. Commun.* **2008**, 990-992. d) Oi, S.; Watanabe, S.-i.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665-8668.

[76] Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837-860.

[77] Comins. D.L. *Synlett* **1992**, 615-625.

[78] Nerdinger, S.; Kendall, C; Cai, X.; Marchart, R.; Riebel, P.; Johnson, M.R.; Yin, C.-F.; Henaff, N.; Eltis, L.D.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 5960-5967. Graves, C.R.; Zhou, H.; Stern, C.L.; Nguyen, S.T. *J. Org. Chem.* **2007**, *72*, 9121-9133. Zhou, J.; Lobera, M.; Neubert-Langille, B.J.; Snider, B.B. *Tetrahedron* **2007**, *63*, 10018-10024.

[79] a) For the D*o*M of secondary benzamides see: Epsztajn, J.; Andrzej, S.; Aleksandra, K. *Curr. Org. Chem.* **2006**, *10*, 1817-1848. b) For their direct arylation see: Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947-4949.

[80] Posner, G.H.; Canella, K.A. *J. Am. Chem. Soc.* **1985**, *107*, 2571-2573.

[81] a) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123-3125. b) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783-1785.

[82] For the metalation of aldimines see for examples: Reichert, S.; Breit, B. *Org. Lett.* **2007**, *9*, 899-902. Flippin, L. A.; Muchowski, J. M.; Carter, D. S. *I. Org. Chem.* **1993**, *58*, 2463-2467. For the metalation of imidazolines: Houlihan, W.; Kelly, L.; Pankuch, J.; Koletar, J.; Brand, L.; Janowsky, A.; Kopajtic, T. A. *J. Med. Chem.* **2002**, *45*, 4097-1409. Houlihan, W. J.; Parrino, V. *J. Org. Chem.* **1980**, *47*, 5177-5180.

[83] Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046-4048.

[84] For examples see: Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1150-1160. Turner, J. A. *J. Org. Chem.* **1991**, *55*, 4744-4750.

[85] Shi, Z.; Li, B.-J.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 5554-5558.

[86] Yang, S.-D.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066-6067.

[87] Li, B.-J.; Yang, S.-D.; Shi, Z.; *Synlett* **2008**, *7*, 949-957.

[88] Fu, J.-m.; Zhao, B.-p.; Sharp, M.J.; Snieckus, J. *J. Org. Chem.* **1991**, *56*, 1683-1685. For mechanistic details, see ref. 4c.

[89] Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424-426.

[90] Tilly, D.; Samanta, S.S.; De, A.; Castanet, A.-S.; Mortier, J. *Org. Lett.*, **2005**, *7*, 827-830. Tilly, D.; Samanta, S.S.; Castanet, A.-S.; De, A.; Mortier, J. *Eur. J. Org. Chem.* **2006**, 174-182.

[91] Fu, J.-m.; Snieckus, V. *Can. J. Chem.* **2000**, *78*, 905-919. Fu, J.-m.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459-5462.

[92] Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 4879-4882.

[93] Zhao, Z.; Jaworski, A.; Piel, I.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2617-2620.

[94] Familoni, O.B. Ionica, I.; Bower, J.F.; Snieckus, V. *Synlett*, **1997**, 1081-1083.

[95] Beaulieu, F.; Snieckus, V. *J. Org. Chem.*, **1994**, *59*, 6508-6509.

[96] MacNeil, S.L.; Gray, M.; Briggs, L.E.; Li, J.J.; Snieckus, V. *Synlett*, **1998**, 419-421.

[97] Gray, M.; Chapell, B.J.; Taylor, N.J.; Snieckus, V. *Angew. Chem., Int. Ed.*, **1996**, *35*, 1559-1560.

[98] For applications of DreM to total synthesis of natural products see: Slana, G.B.C.A.; de Azevedo, M.S.; Lopes, R.S.C.; Lopes, C.C.; Cardoso, J.N. *Beilstein J. Org. Chem.*, **2006**, *2*, 1.; Kalinin, A.V.; Reed, M.A.; Norman, B.H.; Snieckus, A. *J. Org. Chem.*, **2003**, *68*, 5992-5999. Nopporn, T.; Ruchirawat, S. *Synlett*, **2003**, 1037-1039.

[99] a) Smith, M. B.; March, J. *March's Advanced Organic Chemistry, Reaction, Mechanism, and Structure* Wiley, New York, **2001**, Ch. 11. Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, Chichester, **1990**.

[100] Terrier, F. *Nucleophilic Aromatic Displacement: The Influence of the Nitro group*, John Wiley & Sons, New York, **1991**.

[101] Donskaya, O. V.; Dolgushin, G. V. and Lopyrev, V. A. *Chem. Het. Comp.* **2002**, *38*, 371-384. Mąkosza, M. and Kwast, A. *J. Phys. Org. Chem.* **1998**, *11*, 341-349. Chupakhin, O. N.; Charushin, V. N.; van der Plas, H.C. *Nucleophilic Aromatic Substitution of Hydrogen* , Academic Press, San Diego, **1994**.

[102] On the other hand, the scope of VNS requires expansion and S_NAr processes find limited applicability in their high dependency on EWGs situated *ortho* and *para* to the leaving group.

[103] Sibi, P.M.; Chattopadhyay, S. Dankwardt, J. W.; Snieckus, V. *J. Am. Chem. Soc.* **1985**, *107*, 6312-6315. Mills, R.J.; Taylor, N.J. and Snieckus, V. *J. Org. Chem*. **1989**, *54*, 4372-4385. Butenschoen, H.; Winkler, M.; Vollhardt, K. P. C. *Chem. Commun.* **1986**, 388-390.

[104] Kelly, T.R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.*, **2000**, *2*, 3735-3737. Overman, L. E.; Peterson, E.A. *Angew. Chem. Int. Ed.* **2003**, *42*, 2525-2528. de Frutos, Ó.; Atienza, C.; Echavarren A.M. *Eur. J. Org. Chem*. **2001**, 163-171. Elliott, E.L.; Bushell, S.M.; Cavero, M.; Tolan, B.; Kelly, T.R. *Org. Lett.*, **2005**, *7*, 2449-2451. Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H.-J. *Tetrahedron*, **2003**, *59*, 3201-3217.

[105] Zhao, Y.G.; Unpublished results, Queen's University, 2005.

[106] McCubbin, J.A.; Xia, T.; Wang, R.; Zhao, Y.; Snieckus, V.; Lemieux, R.P. *J. Am. Chem. Soc.* **2004**, *126*, 1161-1167.

[107] Kurti, L. and Czako, B., Elsevier Academic Press, San Diego, **2005**, pp.420-421.

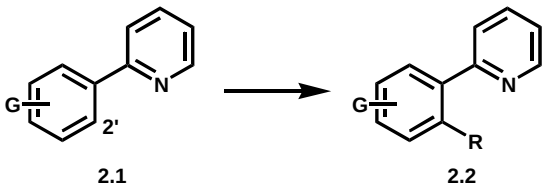
CHAPTER 2

Directed *ortho* Metalation-Boronation and Suzuki-Miyaura Cross Coupling of Pyridine Derivatives: A One-Pot Protocol to Azabiaryls

2.1. Syntheses of Azabiaryls

Azabiaryls have attracted attention not only as valuable intermediates towards several classes of compounds, including carbolines and fluorenones, but also for their own properties useful in medicinal chemistry,[1a] agrochemistry[1b] and material science.[1c] Recently, a particular interest for 2-azabiaryls has been sparked by their applications as substrates for emerging and promising C-H activation processes that allow direct *ortho* arylation,[2a] amination,[2b] hydroxylation,[2c] carbonylation,[2d] chlorination[2c] and silylation[2e] (Table 2.1).

Table 2.1 Functionalization of 2-Phenyl Pyridines via Transition Metal-Catalyzed C-H Activation



2.1 2.2

Catalyst / Reagent	R	Yld (%)
$Rh_4(CO)_{12}$/ CO / CH_2=CH_2	COEt	66-16
$Cu(OAc)_2$ / H_2O / O_2	OH	43-77
$Cu(OAc)_2$ / $ClCH_2CH_2Cl$	Cl	30-92
$Cu(OAc)_2$ / $ArNH_2$	ArNH	17-65
$[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ / ArX	Ar	40-95
$RhCl(PPh_3)_3$ / Ar_4Sn	Ar	36-78
$Ru_3(CO)_{12}$ / $HSiEt_3$	$SiEt_3$	61-79

By virtue of their coordination with the ring nitrogen, copper, ruthenium and rhodium catalysts are capable of activating the 2'-position, avoiding the need for any sacrificial group at that site. However, a variable degree of bis-substitution has been observed which may be expected to be minimized as the methodology moves towards a mature stage of development. In this section, some of the known syntheses of

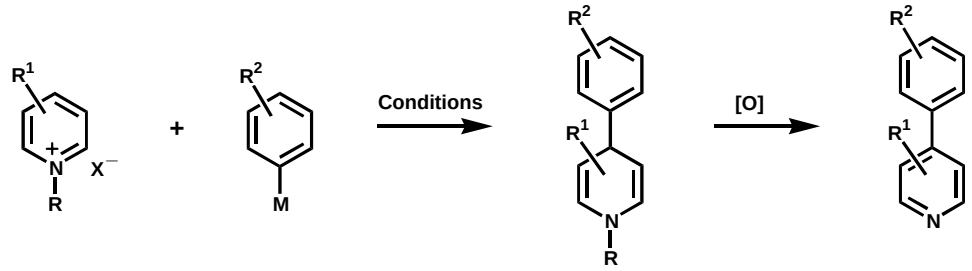
(hetero)arylpyridines will be discussed grouped in 4 categories: non-catalyzed cross-couplings of aromatic rings, non-catalyzed methods for the formation of the pyridine ring, catalyzed methods for the construction of the pyridine ring and transition metal catalyzed cross couplings of aromatic partners.

2.1.1. Non-Catalyzed Cross-Couplings of Aromatic Rings

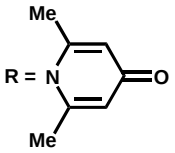
The π-deficient character of the pyridine ring suggests that its arylation may be achieved through nucleophilic attack by an arylmetalloid followed by oxidation of the dihydropyridine obtained. The reaction with aryllithium reagents, which add selectively to the 2- position of the pyridine ring, has not been systematically explored and generally suffers from low yields that have prevented it from acquiring synthetic significance.[3] With the exception of a handful of substituted pyridines,[4] aryl Grignards add with low selectivity to the 2- and 4-positions in low yields. The low reactivity of the pyridine ring towards these nucleophiles has been successfully circumvented by using quaternary pyridinium salts. In this case, nucleophilic addition leads to intermediate dihydropyridines which, upon traceless aromatization through removal of a good leaving *N*-substituent, allows ready access to aryl pyridines. To address the poor regioselectivity of their addition, Grignard reagents have been used with pyridinium salts bearing bulky *N*-substituents which effectively shield the 2-position[5] (Entries 1 and 3, Table 2.2). Alternatively, the less hindered *N*-acyl- and *N*-ethoxy or *N*-phenoxycarbonyl groups are synthetically useful when utilized in coupling with the less reactive organocopper[6] (entry 2), lithium cuprates[7] (entry 5) and mixed copper-zinc[8] aryl organometallic reagents (entry 4). The latter offer a non-negligible advantage in their compatibility with Grignard-sensitive functionalities. All of the reactions in Table 2.2 were carried out in

one-pot with *in situ*-generated quaternary salts and, with few exceptions, displayed a remarkable regioselectivity (> 99:1). Pyridine *N*-oxide is also susceptible to attack by arylmagnesium bromides to give aryl-substituted pentadienal oximes which, upon ring closure with Ac_2O, furnish 2-arylpyridines.[9]

Table 2.2 Synthesis of Phenyl Pyridines *via* Nucleophilic Addition of Aryl Metal Species to Pyridinium Quaternary Salts

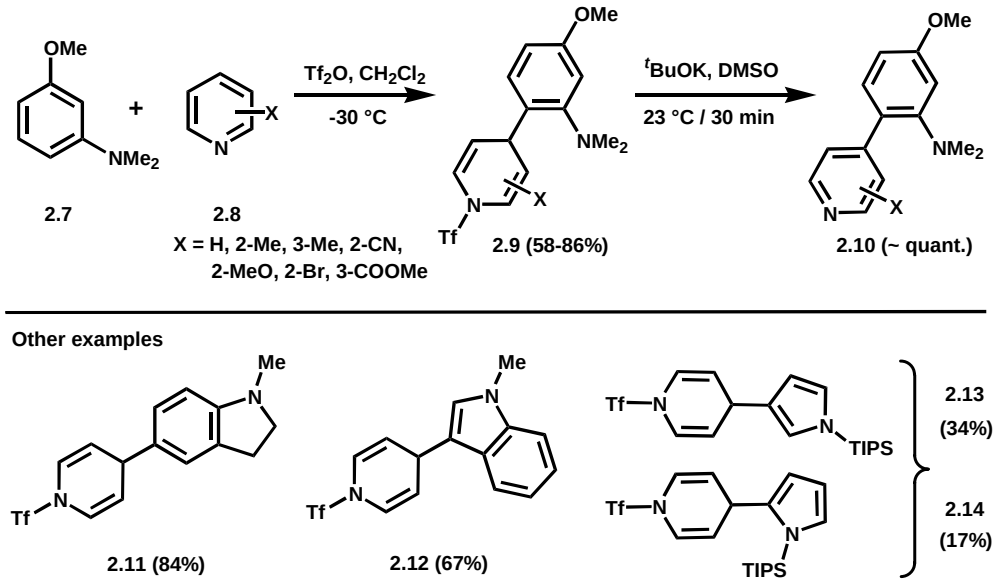


2.3 2.4 2.5 2.6

Entry	R, R^1	R^2, M	Conditions	Yld (%)	Ref.
		M = MgBr			
1	R^1 = H, 3-Me	R^2 = H, 2-Me, 4-Me, 3-MeO,4-MeO, 4-Cl, 4-Br, 2-thienyl	rt /THF / 70 h	35-73	5
2	R = $COCH_3$, COOEt COOPh R^1 = H, 2-Me, 3-Me	R^2 = H, 2-MeO	CuI(5 mol%) / THF/-20 °C/ 15 min	65-86	6
3	R = Si^tBuMe_2 R^1 = H	R^2 = H	rt / THF / 3 h	73	5
		M = Cu(CN)ZnI			
4	R = COOEt R^1 = 4-CN, 4-COOMe, 2-COOMe	R^2 = 3-Me, 3-F, 3-Br 3-COOMe, 3MeO, 3-CN, 3,5-diMe	-55 °C / THF / 1h	29-60	8
5		M = ½ CuLi			
	R = COOMe R^1 = H	R^2 = H, 4-Me,	-78 °C / THF / 0.5 h then 0 °C / 0.5 h	65-70	7

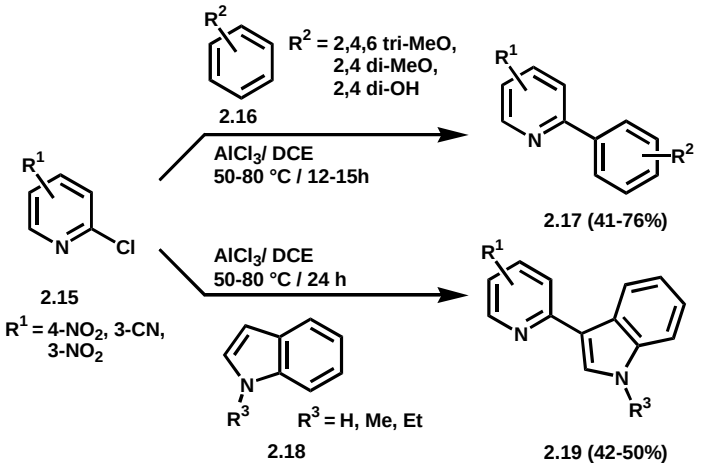
As shown recently by E.J. Corey, *N*-triflated pyridines, generated *in situ*, are so powerfully activated that they couple readily and under mild conditions with neutral π-basic aromatic compounds (Scheme 2.1).[10] With some exceptions, the steric effect of the

triflic group ensures complete regioselectivity in the formation of the intermediate *N*-triflyl-4-aryldihydropyridines **2.9**, which can be quantitatively aromatized with ^{t}BuOK.



Scheme 2.1

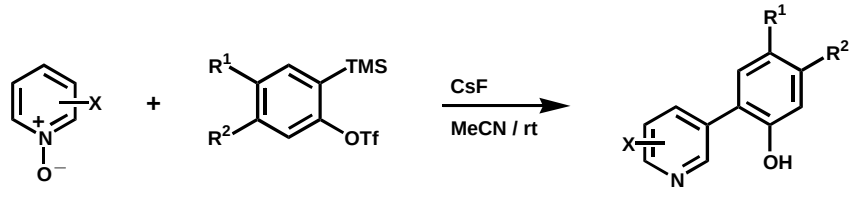
Conceptually similar to Corey's protocol is a recently developed synthesis of 2-arylpyridines involving attack of $AlCl_3$-activated substituted 2-chloropyridines by electron-rich aromatic compounds (Scheme 2.2).[11] However, as demonstrated by the non-reactive 2-chloropyridine, the method is limited to EWG-bearing chloropyridines **2.15** and affords decreasing yields of products as the nucleophilicity of the coupling arenes decreases. In 1974, Abramovitch reported a reaction between benzyne and pyridine *N*-oxides to afford low yields of hydroxyphenylpyridines.[12] Larock revisited this reaction and, by applying his original preparation of benzynes from *o*-(TMS)aryl triflates,[13] developed a general regioselective synthesis of 3-arylpyridines **2.22** (Table 2.3).[14]



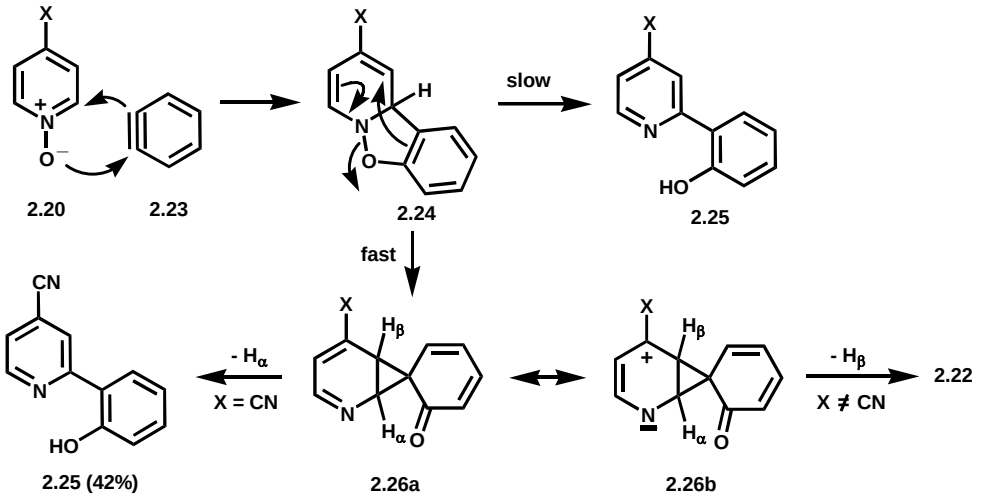
Scheme 2.2

However, regioselectivity becomes an issue when unsymmetrical benzyne precursors are used (R^1 = Me, MeO, F, R^2 = H). The working mechanism postulated by the authors considers the higher acidity of H_β as suggested by structure **2.26b** and its preferential loss leading to the 3-(hydroxyphenyl)pyridines **2.22** observed (Scheme 2.3). Since **2.26b** is unfavourable when X = CN, 4-cyano-pyridine *N*-oxide preferentially looses H_α and gives the 2-arylpyridine **2.25**.

Table 2.3 Synthesis of Aryl Pyridines from Benzyne Precursors and Pyridine *N*-Oxides



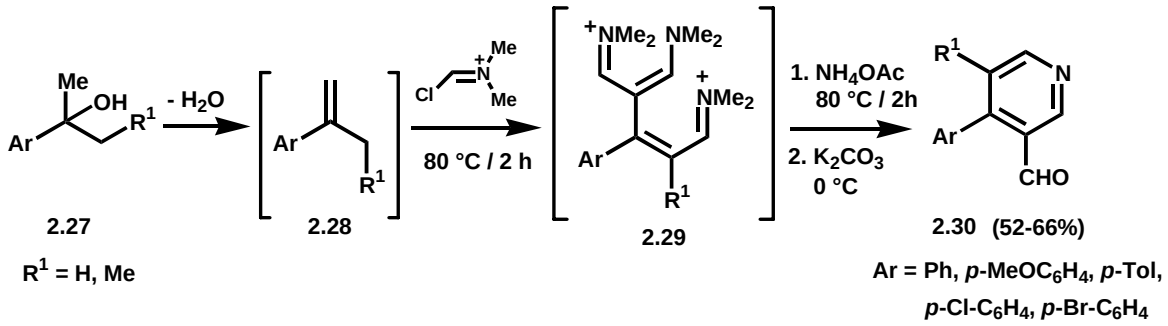
2.20	2.21	2.22
X = H, 2-5 diMe, 4-Me	$R^1 = R^2$ = H, Me, MeO, $CH_2(CH_2)_2CH_2$, F	52-92%
X = H	R^1 = MeO, Me, F R^2 = H	75-83% (1:1 - 2:1)



Scheme 2.3

2.1.2. Non-Catalyzed Methods for the Construction of the Pyridine Ring

The syntheses of arylpyridines discussed in this section have in common the late formation of the pyridine ring from other sources of nitrogen. They have, therefore, been selected from the vast literature describing the *de novo* synthesis of arylpyridines[15] Described in Scheme 2.4 is a straightforward one-pot procedure to 4-phenylnicotinaldehydes[16] developed through improvement and generalization of an old reaction.[17] Here, tertiary alcohols **2.27**, obtained through standard methods, undergo dehydration under the Vilsmeier-Haack conditions, and the styrene intermediates undergo reaction *in situ* with chloromethyleneiminium salt to give five-carbon units **2.29** containing terminal electrophilic centres. Treatment with ammonium acetate furnishes pyridinyl iminium salts which, on hydrolytic work up, afford valuable functionalized nicotinaldehydes **2.30**. The accessibility of arylpyridines through oxidation of dihydropyridines[18] opens a vast array of synthetic options based on elaborations of the Hantzsch synthesis.[19]



Scheme 2.4

While the Hantzsch reaction was discovered as a one-pot synthesis of symmetric dihydropyridines, its flexible variations can furnish unsymmetrical products through stepwise combination of the reagents. Furthermore, by condensing reagents at higher oxidation state such as pyridinium salts,[20] hydroxylamine[21] or ynones,[22] arylpyridines may be obtained without the final oxidative step (Fig. 2.1). In a recent solventless elaboration of the Hantzsch synthesis, generally high yields of 2,4,6-triarylpyridines were obtained with an unsophisticated method consisting in the stepwise addition, mixing and manual grinding of the reagents (Scheme 2.5).[23] The 1,5-diketones obtained undergo sequential condensation with NH_4OAc in hot acetic acid and oxidization to give a rich collection of triarylpyridines.

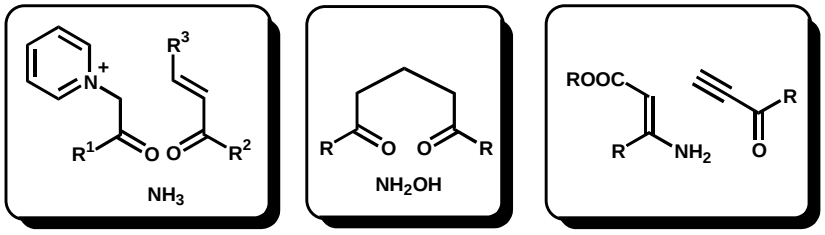
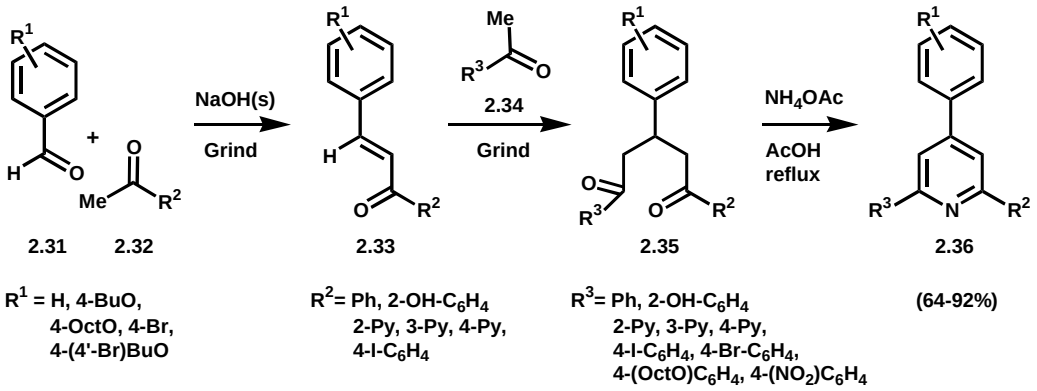


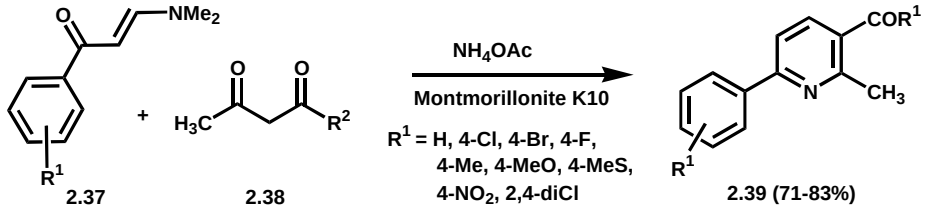
Figure 2.1 Modifications of the Hantzsch Reaction

Remarkably, 2,6-difuryl-4-aryl-pyridines, obtained in excellent yields with standard methods, can be oxidized by $KMnO_4$ to the corresponding 2,6-dicarboxylic acids and, through decarboxylation of the latter, represent a precursor, albeit not an atom economic one, for the construction of simpler 4-arylpyridines (31-58% overall yield).[24]



Scheme 2.5

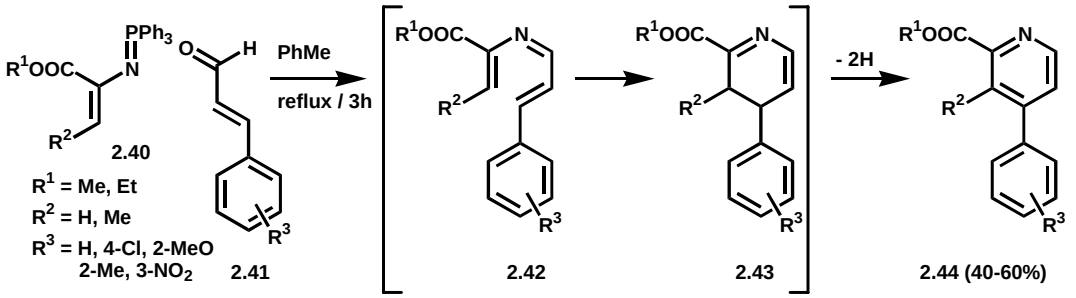
In another Hantzsch-derived approach which furnishes 6-arylpyridines **2.39** in good yields, acetophenone Mannich bases **2.37** were refluxed with β-diketones **2.38** and NH_4OAc in the presence of a clay as a solid acid catalyst (Scheme 2.6).[25]



Scheme 2.6

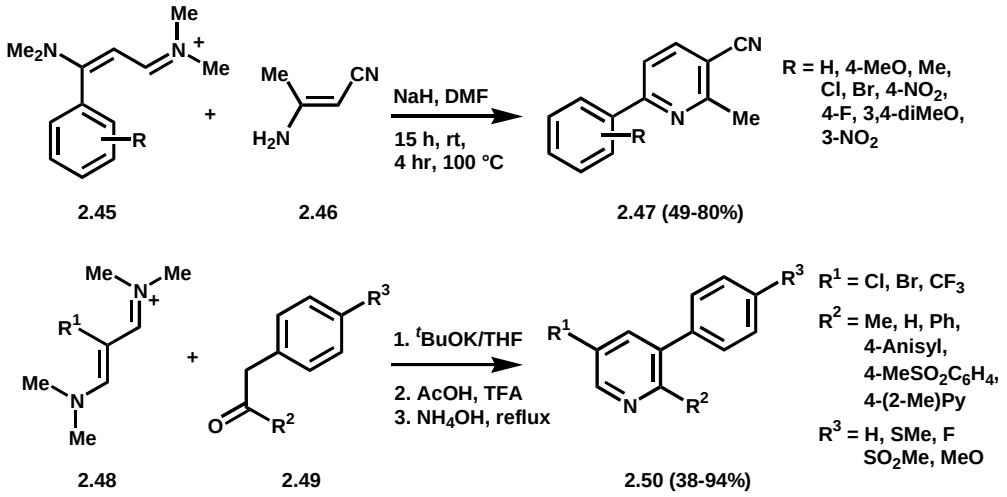
4-Arylpyridines have also been accessed by electrocyclization of azatrienes **2.42** whose N=C bond was formed through an aza-Wittig reaction of α,β-unsaturated aldehydes **2.41** with iminophosphoranes **2.40** (Scheme 2.7).[26] These starting materials, obtained in high

yields (>80%) by subjecting acrylates to the Staudinger reaction, provided moderate yields of 4-aryl and heteroarylpyridines **2.44**.



Scheme 2.7

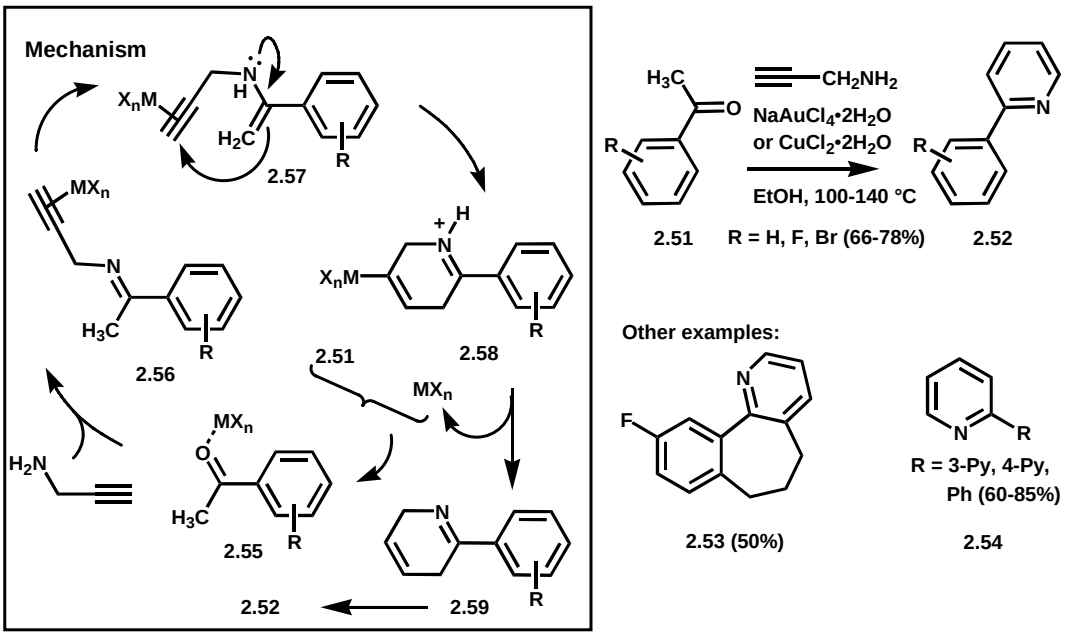
Other syntheses have been based on the condensation of vinamidinium salts **2.45** and **2.48** with enaminonitriles **2.46** or α-aryl ketones **2.49,** respectively, as a source of two-carbon synthons.[1a-ii,27] Scheme 2.8 synthetically shows the scope of these approaches to 6- and 3-arylpyridines **2.47** and **2.50**, respectively.



Scheme 2.8

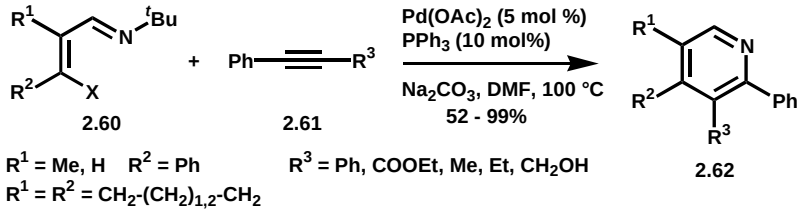
2.1.3. Catalytic Methods for the Construction of the Pyridine Ring

In the last decades, the widespread use of transition metal catalytic processes has also affected the availability of methods for the production of azabiaryls. However, unlike the many classic cyclocondensations which have been developed, few of the catalytic methods involve the assemblage of the pyridine ring from smaller unsaturated units. One of these uses gold or copper salts to cyclize aromatic ketones **2.51** with propargylamine and furnish 2-arylpyridines **2.52** (Scheme 2.9).[28] A plausible mechanism involves a) metal salt-catalyzed formation of the imino intermediate **2.56** followed by isomerization to the enamine **2.57** (the carbonyl compound must therefore be enolizable), b) regioselective 6-*endo-dig* intramolecular nucleophilic attack to form the organometallic intermediate **2.58**, c) protonolysis of the C_{sp2}-M bond to give dihydropyridine **2.59** and regenerate the catalyst, d) final aromatization to **2.52**.



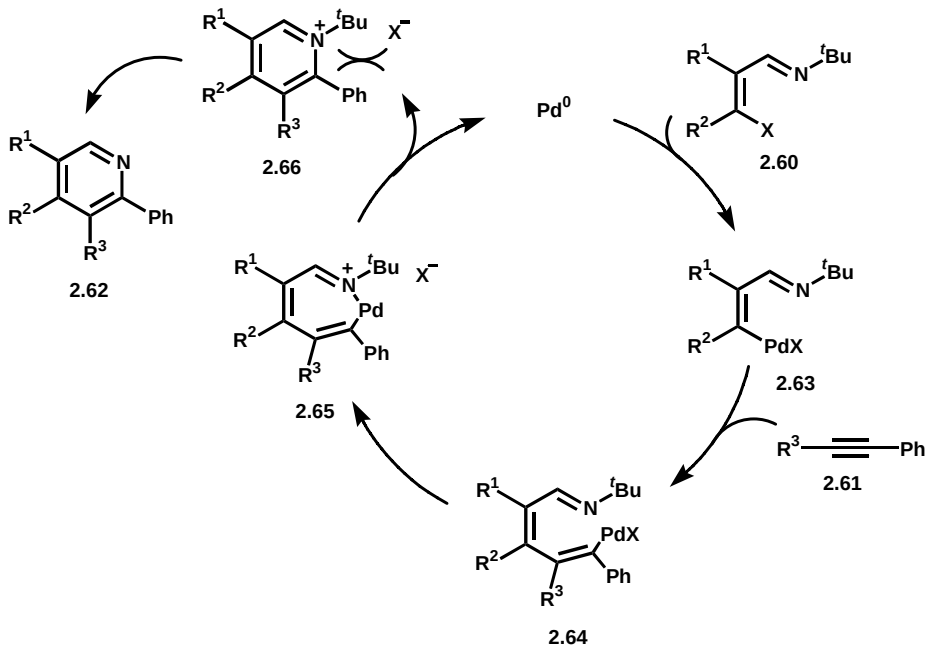
Scheme 2.9

Within this section can also be mentioned the Pd-catalyzed iminoannulation of internal acetylenes derived from the extension of Larock's versatile chemistry.[29] Following this protocol, variously substituted *N*-^{t}Bu-vinylimines **2.60** were regioselectively annulated under Pd catalysis using internal alkynes **2.61** to afford 2-arylpyridines **2.62** (Scheme 2.10).



Scheme 2.10

A likely mechanism follows a similar path to that described for related annulation chemistry.[30] Oxidative addition of the vinyl halide **2.60** to Pd(0) produces an organopalladium intermediate **2.63** which, by inserting the acetylene, is converted into **2.64** (Scheme 2.11). This species undergoes reaction with the neighbouring imine group to form a seven-membered palladacyclic ammonium salt **2.65,** which undergoes reductive elimination to form **2.66** and regenerate Pd(0). Finally, fragmentation of the *N*-^{t}butyl group driven by hindrance or by formation of the ^{t}Bu cation leads to the observed product **2.62**. Catalyzed methods that, like the latter, use C-C or N-C units to assemble the pyridine ring, inevitably afford heavily substituted products and often suffer from limited scope due to the substitution pattern required in the SMs to control the regiochemistry of the reaction. These problems are the main drawbacks in the synthesis of arylpyridines by transition metal-mediated [2+2+2] cycloadditions[31] or by cycloaddition of nitriles with lithiobutadienes,[32] methods which will not be discussed.

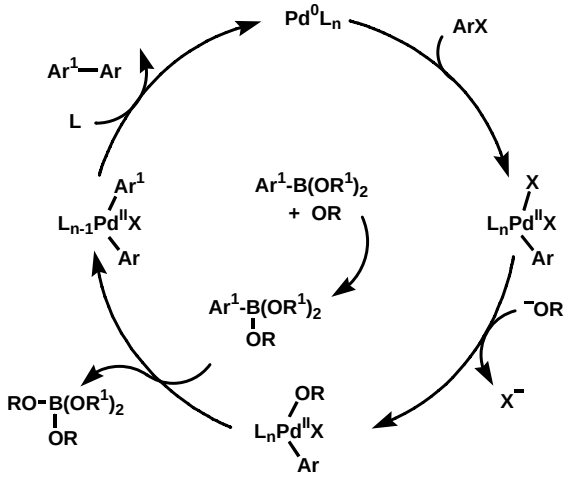


Scheme 2.11

2.1.4. Transition Metal-Catalyzed Cross Couplings of Aromatic Partners

Most of the metal-catalyzed methods to synthesize arylpyridines are based on the direct coupling of halopyridines, many of which are commercially available, and an aryl or heteroaryl metallorganic compound (-SnR_3,[33] -$B(OR)_3$,[34] -ZnX,[35] -MgX,[36] $Si(OR_3)$,[37] In,[38] Table 1.2, where **1.63** is a pyridine derivative). The most popular method is certainly the Suzuki-Miyaura reaction due to the stability (and therefore commercial availability) and low toxicity[39] of arylboronic acids. Other metallorganic compounds (-ZnX, -MgX) require to be freshly prepared (although often *in situ*), necessitate carefully controlled coupling conditions (exclusion of moisture), suffer FG incompatibility (-MgX) or may be toxic and therefore unsuitable for large scale reactions (-SnR_3). As for the alternative approach based on the coupling of metallorganic pyridines with aryl halides, poor experience in the synthesis and isolation of borylated heterocycles has disfavoured

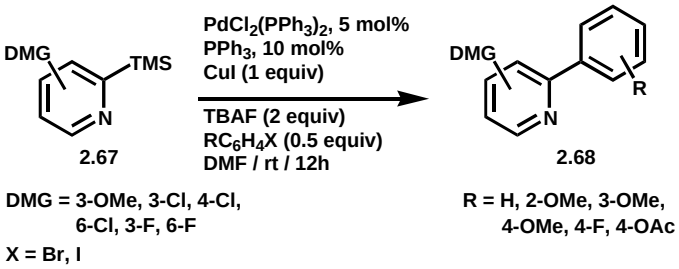
the application of the Suzuki protocol versus the use of the Stille,[40] and, to a lesser extent, the Negishi[41] and the Corriu-Kumada[42] methods.[43] The mechanism of these reactions, shown for the Suzuki coupling in Scheme 2.12, is generally based on three key steps: an initial oxidative addition of the active catalyst to the halide, transmetalation of the metallorganic partner, and a reductive elimination final step that ejects the cross coupled product and regenerates the catalyst.



Scheme 2.12

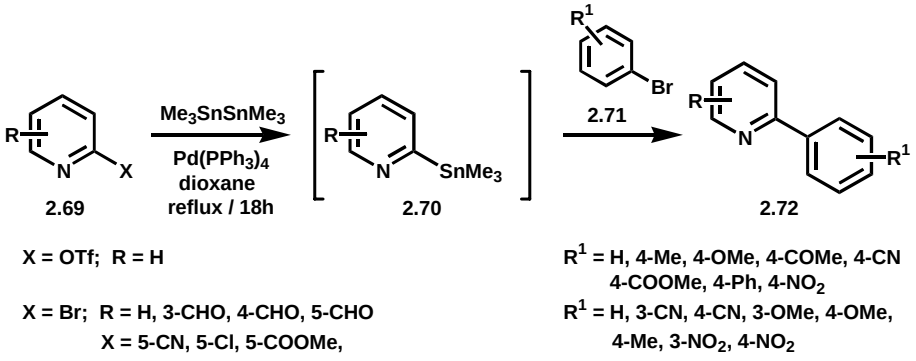
The specific synthesis of 2-arylpyridines, complicated by the instability of 2-pyridinyl boronic acid,[44] can be approached through the use of pyridinylsilanes which have been rarely preferred to the alternative pyridinyl halides as cross coupling partners.[45] Recently, Fort has reported that 2-TMS-pyridines **2.67** undergo cross coupling with aryl iodides and bromides under Pd-Cu co-catalysis to give azabiaryls **2.68** (Scheme 2.13).[46] The easy access to these silyl-pyridines by D*o*M makes this approach an effective link between D*o*M and the Hiyama coupling methodology. Although the scope of this protocol is limited to 2-pyridyl arenes (**2.68**), this method acquires a high significance in

view of the low reactivity of pyridinyllithium reagents towards tetraethyl orthosilicate $Si(OEt)_4$[47] to give the corresponding siloxanes, a fact which has weakened the HetDoM-Himaya nexus.



Scheme 2.13

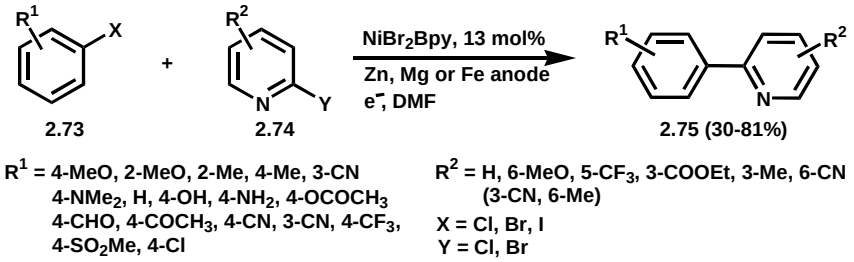
2-Azabiaryls such as **2.72** have been obtained in a convenient one-pot version of the Stille coupling of 2-Br and 2-OTf pyridines **2.69** with a variety of het(aryl) bromides **2.71** (Scheme 2.14).[48] The successful minimization of homocoupling processes is due to the high reactivity of 2-halopyridines in the oxidative insertion of Pd(0), not only *vis a vis* 3- and 4-brominated[49] or triflated pyridines,[50] but also against the C-Br bond of the coupling partners.



Scheme 2.14

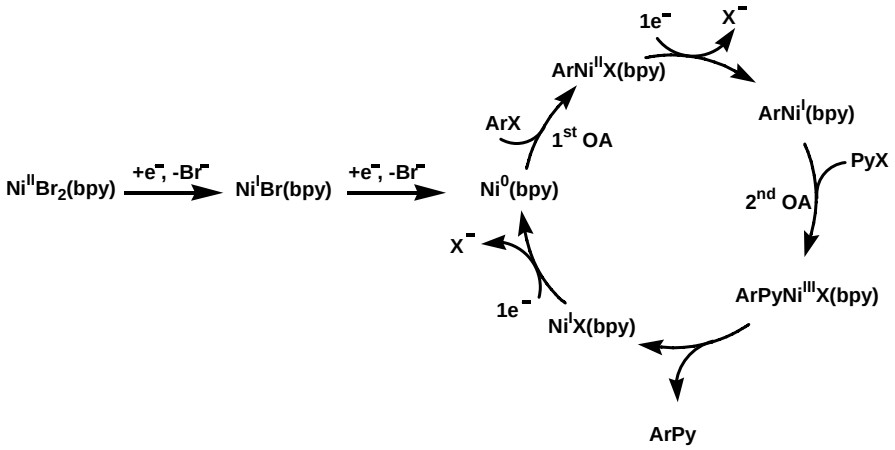
Thus, the initial rapid formation of a pyridylstannane **2.70** in the presence of the less activated, bystander bromides, is followed by standard oxidative addition of the latter to

Pd(0), transmetalation with the stannane and reductive elimination to afford the 2'-arylpyridines **2.72**. On a similar concept is based the Ni-catalyzed electroreductive coupling of aryl halides **2.73** with 2-halopyridines **2.74** to give azabiaryl **2.75**[51] whose mechanism is based on two sequential oxidative addition steps (Schemes 2.15 and 2.16).

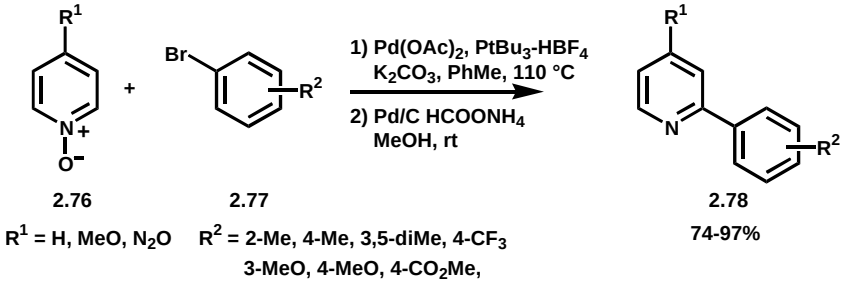


Scheme 2.15

However, unlike in the one-pot Stille coupling (Scheme 2.14), voltammetric measurements have shown an inverse order of reactivity of the aryl halides towards electrogenerated Ni(0)bpy, with most bromobenzenes reacting in the first oxidative addition step (1st OA) and 2-chloro or bromopyridines in the second one (2nd OA, Scheme 2.16). Thus, homocoupling is kept under effective control, unless the effect of substituents on the respective partner rings (for example EWGs on the pyridine and EDGs on the aryl bromide) may invert their reactivity in the oxidative addition step, leading to bipyridines. In these rare cases, the required balance of reactivity can be re-established by using the more reactive aryl iodides and the less reactive pyridyl chlorides. The latter is an interesting example of the contribution that electrochemistry, often neglected in synthesis, may offer to the development of organic reactions. An interesting avenue to 2-arylpyridines has been recently opened by Fagnou's work, which has established the conditions for a very efficient Pd-catalyzed regioselective direct arylation of pyridine *N*-oxides with aryl bromides (Scheme. 2.17).[52]



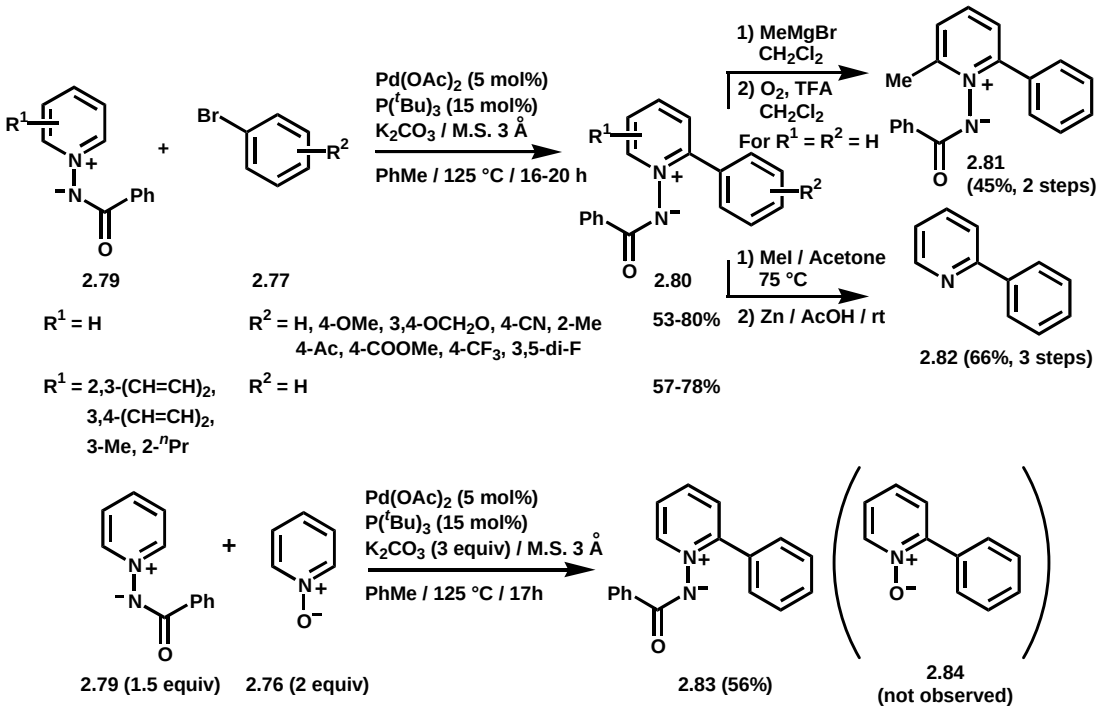
Scheme 2.16



Scheme 2.17

Despite the need for 4 equivalents of the *N*-oxide, the strength of the method lies in the use of inexpensive, commercially available and shelf-stable materials. Subsequent Pd-catalyzed reduction with ammonium formate leads, in high yields and under mild conditions, to the 2-arylpyridines **2.78**. Recently, Charette has reported a similar approach to 2-aryl pyridines which requires only a small excess (1.5 equiv) of the pyridine derivative. Thus *N*-iminopyridinium ylides **2.79** undergo Pd-catalyzed direct arylation with electron-rich and electron-poor aryl and heteroaryl bromides (Scheme 2.18). The *o*-arylated ylides (**2.80**) can be further functionalized at C_6 (**2.81**) or undergo reductive cleavage of the *N*-*N* bond to give 2-arylpyridines (**2.82**). Interestingly, an intermolecular competition experiment between **2.79** and pyridine *N*-oxide (**2.76**)

suggests that the amide functionality of **2.79** is a stronger directing group than the *N*-oxide.



Scheme 2.18

2.2. *Ortho* Metalation of DMG-Bearing Pyridine Systems

In the early 1970s, while the development of D*o*M in aromatics was already in full gear flight, the exploration of the *ortho*-metalation of π-deficient heteroaromatics stood still on the runway. One reason was the readiness of these low LUMO-level substrates to undergo, even at low temperatures, nucleophilic attack at the C=N bond by alkyllithium reagents. However, the proven vocation of pyridines for the synthesis of biologically active molecules has called for a wide screening of metalation conditions and suitable bases, which have culminated in providing clean, selective metalation and introduction of a plethora of electrophiles. Due to the effect of the nitrogen atom, the p*K* values of the pyridine protons are estimated to be slightly lower than those of benzene (p*K* 43) but

higher than 36, the value of diisopropylamine (DIPA).[53] In the presence of electron-withdrawing DMGs (I, Cl, Br, F, $CONR_2$, SOR, CN, …) whose inductive effects increase proton acidity and ring sensitivity to nucleophilic attack, hard, non-nucleophilic bases like LDA (pK 35.7)[54] or the stronger LiTMP (pK 37.3)[55] are generally the first choices to effect deprotonation without the interference of metal-halogen exchange and ring addition processes. However, the successful metalation of 2,4-dichloro-,[56] 3,5-difluoro-[57] and 2-chloro-5-bromopyridine[58] with alkyllithiums, to quote only a few examples, suggests that the use of soft bases with disubstituted pyridines should not be dismissed without testing. With strong coordinating DMGs (NHCOR, $OCONR_2$, CONHR) and in other substitution-dependent cases (DMG = Cl, OR, F) where LiTMP does not effect deprotonation, the soft alkyllithiums can still be used successfully with the proviso of applying carefully controlled reaction conditions. Finally, highly electron-rich pyridines can be likened to benzenes due to their high LUMO energy and, as demonstrated for several dialkoxypyridines, may be safely metalated with unhindered alkyllithiums at relatively high temperatures (0 °C – rt).[59] The metalation of pyridines bearing C_3-DMGs poses the question of regioselectivity since lithiation may in theory occur at C_2 or C_4. The relative rates of hydrogen-deuterium exchange of pyridine, as measured by Zoltewicz in CD_3OD-CD_3ONa at 164.6 °C, are 1.0 : 9.3 : 12 for H_2, H_3 and H_4 respectively.[60] With some differences in the ratios, similar patterns can be found in other solvents (1 : 2.3 : 3.0 in D_2O-NaOD at 200 °C[61] and 1.0 : 72 : 240 in NH_3-$NaNH_2$ at –30 °C)[62] and appear consistent with similar measurements carried out for 3-Cl-pyridine (1 : 53 = H_2 : H_4 in CD_3OD-CD_3ONa at 110.2 °C)[63] and with evidence that dehydrohalogenation of *meta*-halopyridines furnishes only 3,4- and not 2,3-pyridyne.[64]

Contrary to expectations solely based upon inductive effects, the ring nitrogen does not facilitate carbanion formation at C_2 to the same degree that it does for more remote centres. The reason for this observation is attributed to two as yet experimentally unverified factors: a) the electrostatic repulsion between the coplanar nitrogen electron pair and the incipient electron pair of the transition state for deprotonation at C_2; b) the *endo* angle at C_2 is 4° larger, and the angles at C_3 and C_4 are 1° 24' and 1° 54' smaller, respectively, than the 120° angle found in benzene.[65] This geometry, which qualitatively applies to 3-fluoropyridine as well,[66] may correspond to a decrease in the s character for the C_2-H bond and, therefore, to a decrease of its acidity, while an opposite but slighter change is expected for C_3 and C_4. Consequently, C_3-DMG bearing pyridines generally undergo deprotonation at C_4, the most acidic site. In several cases, however, metalation of such systems occurs selectively at C_2 or C_4 depending on the experimental conditions, and this regioselectivity may be explained in terms of thermodynamic or kinetic control. In the following section, an updated review of the most important DMGs in the pyridine series is given, limited to the parent compounds in order to discuss observations, case studies, problems and the solutions that have been developed during the progress of the research comprising this thesis.

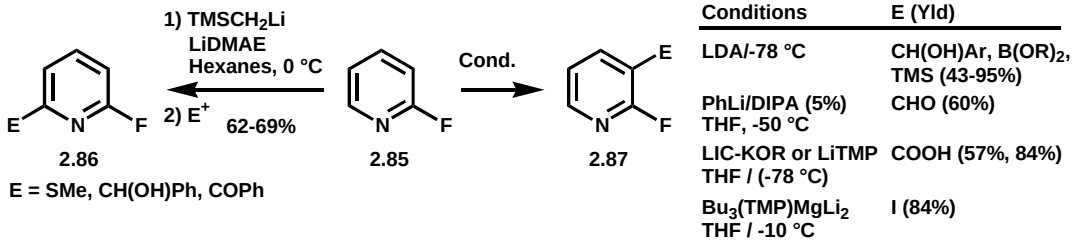
2.2.1. Halogen-based DMGs

The experimental data that follows documents the meticulous attention towards the chemo- and regioselective lithiation of halopyridines which has its rationale in their wide commercial availability or easy synthetic access from other derivatives and, more importantly, in their synthetic versatility by which they can be substrates for metal-

halogen exchange, addition elimination, $S_{RN}1$ and cross coupling reactions. Furthermore, lithiated halopyridines are less prone to decompose to pyridynes compared to aryl halides by elimination of lithium halides. To illustrate, while *o*-fluoro-, *o*-chloro- and *o*-bromophenyllithiums have been prepared by metal-halogen exchange at -60, -90 and -100 °C (the latter only in 23%) respectively,[67] *o*-chloro- and *o*-bromopyridyllithium intermediates are generated at –40 and –78 °C, respectively (see Schemes 1.45-1.47) and 3-fluoro-4-lithiopyridine eliminates LiF only at rt.[68] A large part of what we know about this topic has been uncovered and developed by Quéguiner who has established optimized metalation conditions for an impressive number of halopyridines.[69] Schlosser's research has especially focused on the application of the concept of "regioexhaustive substitution" which asserts affordable access to all isomers of a given di- or polysubstituted halopyridine from a simpler substrate.[70] This is accomplished, although at times through winding pathways, with a restricted set of principles and methods ("toolbox methods"), namely, but not exclusively, ring-walk metalation, site discriminating deprotonation (indicated as "optionally site selective metalation"), metal-halogen exchange, halogenation-dehalogenation, "congestive" protective groups, and basicity gradient-driven iodine migration ("halogen dance"). More recently, Gros and Fort have imparted an original momentum to this topic with the discovery of new metalating agents that allow traditionally disfavoured ring positions to be lithiated and functionalized.

2-Fluoropyridine undergoes *ortho*-lithiation with excellent regioselectivity using LDA,[71] LiTMP,[72] or Schlosser's super base (LIC-KOR)[73] at low temperatures (–78 °C, **2.85** → **2.87**, Scheme 2.19). Only recently, higher temperatures have become applicable with

new non-nucleophilic metalating agents that generate stable metalated intermediates. The use of magnesate $Bu_3(TMP)MgLi_2$ at −10 °C does not result in pyridyne formation but appears to have a narrow scope on 2-fluoropyridine as only iodine quench has been demonstrated.[74] The lithiating agent $TMSCH_2Li$/LiDMAE (**2.85** → **2.86**) is the result of the optimization of Gros and Fort's original ^{n}BuLi/LiDMAE ($Me_2N(CH_2)_2OLi$) system which, in the last decade, has been applied to effect the α-lithiation of pyridines independently from, although often times synergistically with, DMGs on the ring.[75] The formation of aggregates involving LiDMAE, ^{n}BuLi, the ring nitrogen and, when accessible, the DMG of the pyridine substrate improves the basicity/nucleophilicity ratio of the alkyllithium and, by maintaining this base close to the nitrogen, ensures a selective 2-lithiation of the substrate (**2.88**, Fig. 2.2).



Scheme 2.19

While the original system typically requires a three to four-fold excess of ^{n}BuLi/LiDMAE and electrophile (to avoid its consumption by the excess of base) as well as low metalation temperatures (−78 °C) to minimize addition side-reactions, $TMSCH_2Li$/LiDMAE is effective at a 2-fold excess and displays a very low nucleophilicity, allowing the use of more practical conditions. Thus, 2-fluoropyiridine can be metalated at −100 °C[76] with the original Gros and Fort reagent or at 0 °C thanks to the low nucleophilicy of $TMSCH_2Li$ (**2.85** → **2.86**, Scheme 2.19).[77] The requirement of

hexanes or toluene as solvents is noteworthy, as the more common metalation solvents (THF and Et_2O), interfere with the chelate **2.88** in virtue of their coordinative ability.

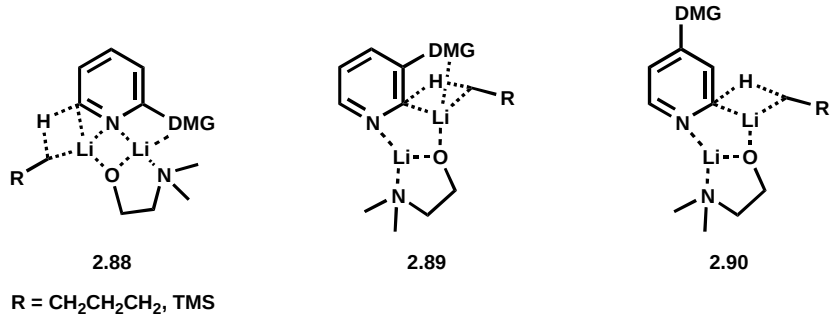
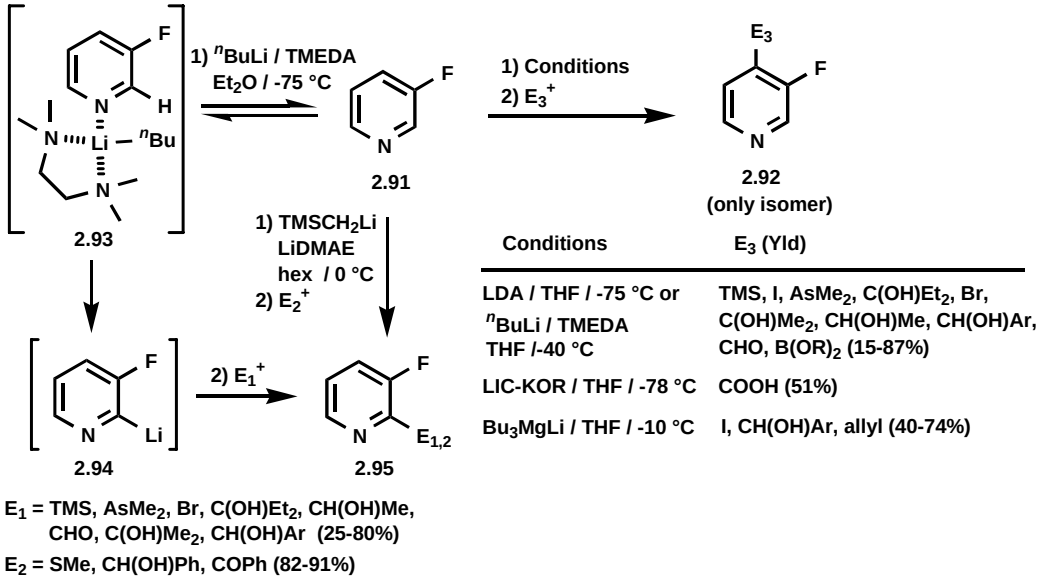


Figure 2.2 Possible Aggregates Involving the Ring Nitrogen in the Metalation of Pyridines with the ^{n}BuLi/LiDMAE Reagent

The metalation of 3-fluoropyridine has been thoroughly studied by Quéguiner who has shown the critical role solvents play in these processes.[78] While LDA[78a,b]and LIC-KOR regioselectively metalate this substrate at C_4 (**2.92**, Scheme 2.20), ^{n}BuLi at –40 °C gives, without competition from nucleophilic side reactions, mixtures of 2-lithio- and 4-lithio-3-fluoropyridine species both in THF and Et_2O. However, while THF favours lithiation at C_4, Et_2O promotes lithiation at C_2, and these effects are heavily reinforced by addition of TMEDA. These observations may be rationalized by a kinetically controlled lithiation at C_2 in Et_2O, following coordination of the base with the pyridine nitrogen (**2.93**)**.** This event may also increase the acidity of H_2 through the amplified inductive effect of the coordinated nitrogen.[79] Quéguiner's calculations, in fact, suggest that as MeLi (a simplified model for ^{n}BuLi) approaches the ring nitrogen of **2.91**, H_2 becomes more acidic than H_4. At higher temperatures or with longer metalation times, the C_2-lithiated species equilibrates to the thermodynamically most acidic C_4-species through the intermediacy of 2,4-dilithio-3-fluoropyridine, which has been trapped as the bis-TMS derivative (yield not reported). Lithiation at C_2 does not occur in THF, probably because

the more basic molecules of this solvent prevent the formation of the chelate **2.93** and the metalation is kinetically controlled at C_4, the most acidic site of free 3-fluoropyridine.

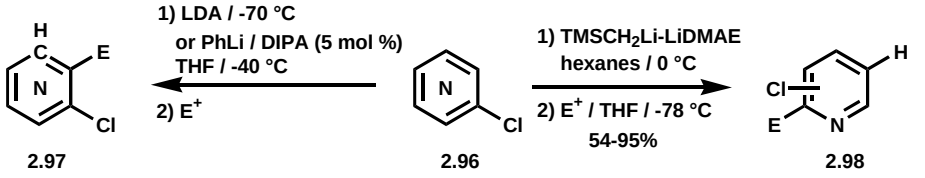


Scheme 2.20

While complete regioselectivity in the C_2-lithiation of 3-fluoropyridine in Et_2O cannot be achieved even at very low temperatures (TMSCl quench gives at best 73% of the 2-TMS derivative and 6% of the 4-TMS isomer), DABCO, used in place of TMEDA, drastically lowers the solubility of **2.94** and hence its isomerization rate, resulting in complete regioselectivity. Recently, process chemists at Merck have reviewed this procedure and made it amenable to the kilogram scale preparation of 3-fluoro-2-carboxylic acid.[80] As for 2-fluoropyridine, the metalation temperatures can be drastically increased for 3-fluoropyridine using $TMSCH_2Li$. The unselective (C_2:C_4 = 53%:45%, TMSCl quench) but quantitative lithiation of 3-fluoropyridine at 0 °C with $TMSCH_2Li$ alone can be effectively cured with the addition of LiDMAE, which strongly favours C_2-deprotonation (**2.91** → **2.95**, Scheme 2.20). The metalation of 3-fluoropyridine with ^{n}BuLi/TMEDA in

Et_2O and with $TMSCH_2Li$/LiDMAE are similar in outcome and mechanism. In both cases, the coordination of the ring nitrogen is critical to the regioselectivity through a chelate, which is sensitive to the coordinative aptitude of the solvent. As with the 2-fluoro isomer, magnesiation (with Bu_3MgLi, -10 °C) makes relatively high temperatures amenable to the C_4-functionalization of 3-fluoropyridine. Although the 4-lithio intermediate may be stable for some time at this temperature, the successful metalation of 3,5-difluorobenzene under the same conditions (with Bu_3MgLi, -10 °C) suggests that the mechanism does not proceed through a pyridyllithium intermediate, but directly via a stable magnesate.

The metalation of chloropyridines (especially the 3-chloro isomer, **2.96→2.97**, Scheme 2.21)[81] has been achieved with generally good results by Gribble under LDA conditions.[82]



2-Cl E = D, TMS, CHO, CH(OH)Ar, Me, allyl, $C(OH)Et_2$, Br, I, $C(OH)Ph_2$, $B(OR)_2$ (30-80%); E = Br, CHO, SMe, COPh, CH(OH)Ph (54-95%)

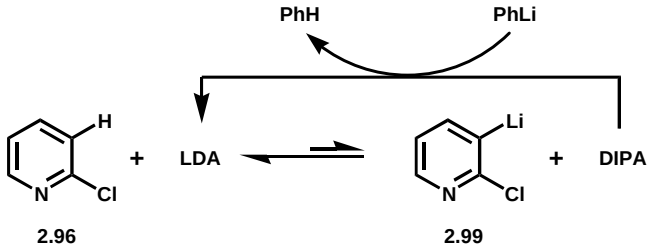
3-Cl E = TMS, I, SPh, CH(OH)Ph, $C(OH)Ph_2$, $B(OR)_2$ (51-96%)

4-Cl E = TMS, $B(OR)_2$ (43-92%)

Scheme 2.21

However, the electrophilic quench of 3-lithio-2-chloropyridine thus obtained, gives low yields of products[83] (*e.g.*, E^+ = DCl, 47%) suggesting that the metalation equilibrium does not strongly favour the lithiated intermediate. This problem has been overcome by Mallet by applying the LDA-catalyzed metalation technique (**2.96→2.97**, Scheme 2.21).[84] This method, also used in the metalation of 2-fluoropyridine, is especially useful

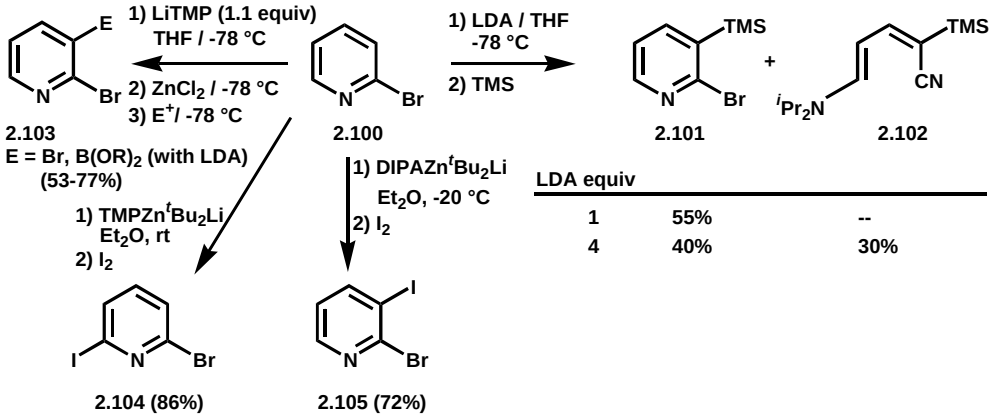
to metalate weakly-acidic substrates (e.g., 2-methoxypyridine, Scheme 2.29) whose *ortho*-lithiated derivatives are formed in very small amounts in equilibrium with DIPA. Thus, small amounts of LDA can be used to obtain high concentrations of the lithiated intermediates **2.99**, as long as DIPA is efficiently removed from the system by irreversible reaction with PhLi (Scheme 2.22). This method is not required for the silylation and boronation of chloropyridines since the base-compatible electrophiles TMSCl and $B(O^iPr)_3$ consume the lithio intermediates as they are formed, driving the reaction to completion.[71b,78b,82b] All isomeric chloropyridines have been α-metalated at –78 °C with ^{n}BuLi/LiDMAE and, with similar results but at 0 °C, with $TMSCH_2Li$/LiDMAE (Scheme 2.21).[77,85] Since 3-chloropyridine undergoes C_4-lithiation with lithium amides, the reversed C_2- regioselectivity of the aminoalkoxide aggregate on this substrate represents a most welcomed result which requires exploitation. This result may well be based on a cooperative effect of the DMGs (3-Cl and ring nitrogen, see **2.89**, Fig. 2.2).



Scheme 2.22

The metalation of bromopyridines has not met with the same success as that seen with chloropyridines, and the methods available have not been generalized. 2-Bromopyridine undergoes C_3 lithiation by LDA in a rapid equilibrium, which precludes efficient trapping of the C3-lithio intermediate by electrophiles (**2.101**, Scheme 2.23). However, when an

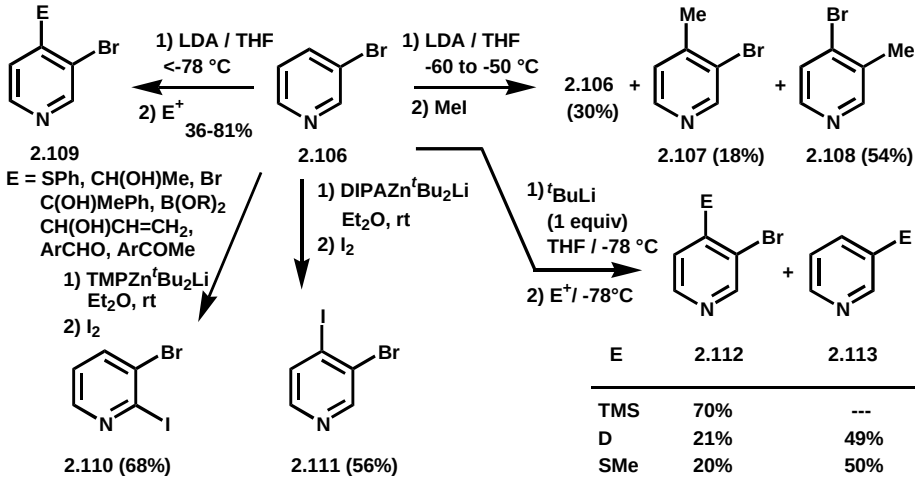
excess of LDA is used to shift the equilibrium towards the lithiated species, the latter succumbs to LDA nucleophilic attack, which triggers a competitive ring opening process (**2.102**).[86] Recently, the *ortho*-bromination and boronation of this substrate has been achieved in moderate to good yield (**2.103**) by using the stronger base LiTMP and transmetalating the pyridyllithium intermediate to an arylzinc species which is then quenched with Br_2 or $B(O^iPr)_3$.[71b,87]



Scheme 2.23

As seen with the magnesates, higher metalation temperatures have been used in Kondo's "regiocontrolled deprotonative zincation" which is based on the use of aminozincates.[88] Under Kondo's conditions, 2-bromopyridine was shown to undergo metalation at C_6 (**2.104**) by zincate TMP-Zn^{t}Bu$_2$Li and at C_3 (**2.105**) by an analogue DIPA-zincate with no formation of 2,3-pyridyne.[89] 3-Bromopyridine may be lithiated by LDA (Scheme 2.24), but the 4-lithio intermediate undergoes intermolecular lithium-hydrogen exchange ("halogen dance", see below) which results in a mixture of regioisomeric products[90] (**2.107** and **2.108**), unless temperatures lower than −78 °C are used (**2.109**).[78b,82b,91] Kondo's metalating agents, instead, allow optionally site selective metalation of 3-

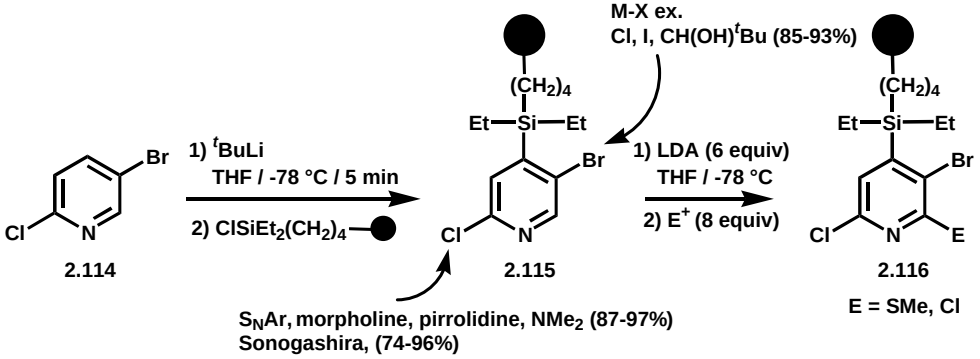
bromopyridine and lead to the selective generation of isomeric 2- and 4-pyridylzincates which are stable at room temperature (**2.110** and **2.111**). Cross coupling of Kondo's arylzincates has been demonstrated under Pd catalysis (Table 1.2); however, no electrophile other than iodine has been shown to be trapped by these intermediates, posing a serious limit to the scope of this methodology.



Scheme 2.24

Recently, in a surprising result, 3-bromopyridine was shown to be cleanly *ortho*-metalated with ^{t}BuLi to give its 4-silylated derivative **2.112** and not, as expected, the product of metal-halogen exchange **2.113** which is observed with ^{n}BuLi. However, the order of addition was found to be critical to the chemoselectivity of the reaction as inverse addition of the reagents totally reversed its outcome, giving **2.113**. A screening of the experimental conditions showed that increasing metalation temperature, time, as well as the number equivalents of base affect the product ratio in favour of M-X exchange and that, in any case, the 4-lithiated intermediate can be trapped selectively only with TMSCl. This suggests the formation of a reactive precursor common to the two pathways, which, depending on the conditions, partially or totally evolves towards 3-

lithiopyridine or, if TMSCl is added,[92] is fully converted into 4-lithio-3-bromopyridine and then rapidly trapped. ^{t}BuLi and ^{s}BuLi have also effected clean *o*-lithiation of 2-chloro-5-bromopyridine (**2.114**, Scheme 2.25), which has been used to illustrate the solid phase metalation of a scaffold with numerous reactive sites for introduction of structural diversity. The silicon-based linker allowed traceless and quantitative cleavage, and the two halogen functionalities were used for double Sonogashira, Stille and Suzuki coupling reactions, ortho-lithiation (Br), S_NAr reactions (Cl) and metal-halogen exchange (Br).[93]

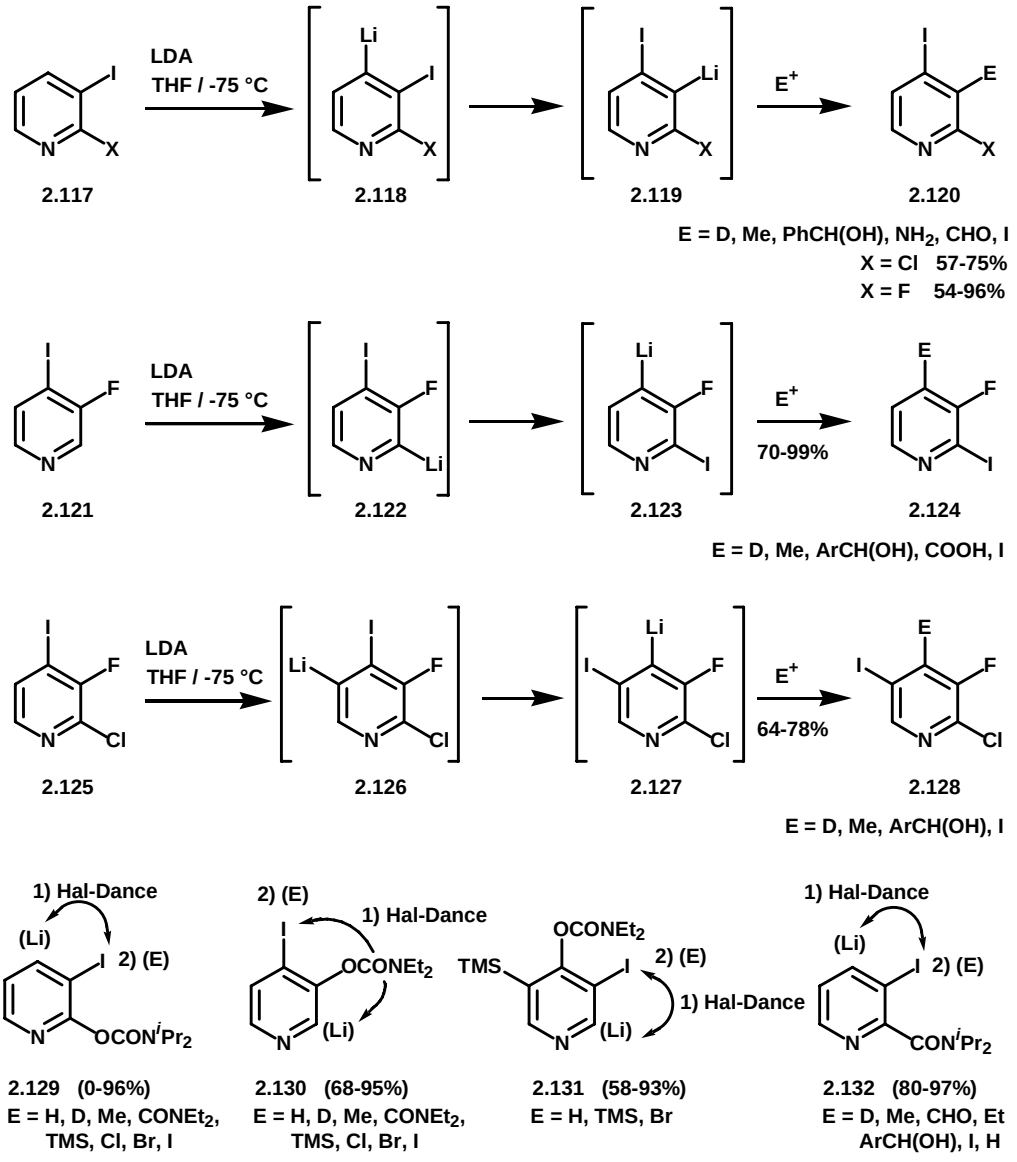


Scheme 2.25

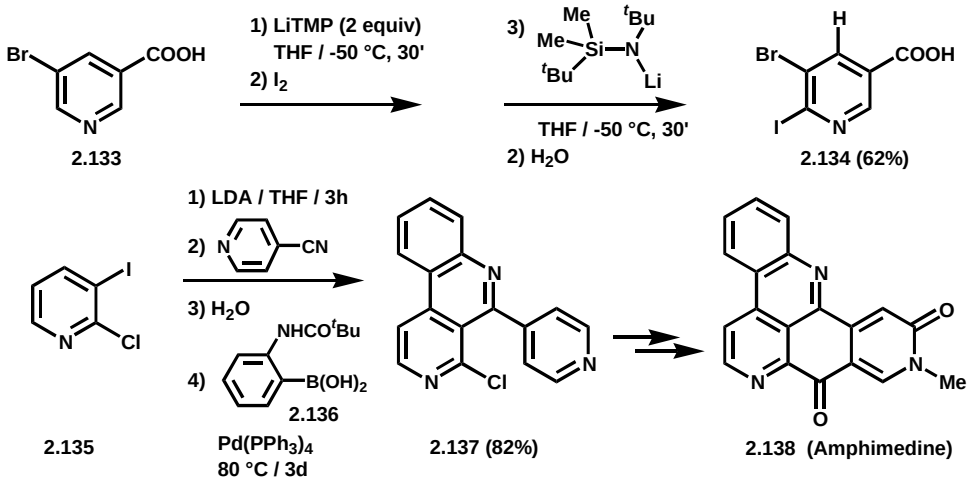
As Gribble reported,[82a] 3-iodopyridine gives fleetingly stable lithio derivatives even at –95 °C and, in fact, the D*o*M of iodopyridines, achievable with LDA or LiTMP, is known only in substrates bearing other substituents. Depending on the metalated position, *ortho*-lithiated iodopyridines easily undergo iodine intermolecular migration leading to more stable isomers. This rearrangement, called the "halogen dance", can be a nuisance at times but, when occurring cleanly, can be turned into a useful synthetic tool.[94] It was with this aim that Quéguiner explored the behaviour of a series of polyhalogenated pyridines and found that, in certain cases, these may be lithiated without decomposition and, before electrophilic quench, undergo rearrangement to the most

stable lithiated species.[95] Thus, the 2-halo-3-iodopyridines **2.117** (Scheme 2.26) were found to form a stable 3-lithiated species **2.119** (owing to synergistic stabilization by two EWG = DMGs) which derives from the rapid isomerization of the C_4-lithio intermediate by halogen dance. The 3-halo-4-iodopyridines **2.121** may follow a similar reaction course; however fluorine directs the formation of a 2-lithiated intermediate which undergoes isomerisation to the more stable 4-lithioderivative **2.123**. Only if the 2-position is already substituted (**2.125**), D*o*M at C_5 is observed followed by isomerization of the C_5-lithio intermediate to the doubly stabilized C_4-anion **2.127**. Recently, the optimization of this reaction on a number of iodopyridines bearing the powerful carbamate group **2.129**-**2.131**, has shown that high dilution and a 30 min metalation time are crucial to achieve high yields in the "dansed" product.[96] The migration patterns mirrored those observed with the polyhalopyridines above and with the 3-iodopicolinamide **2.132** tested by Quéguiner.[97] Remarkably, an *ortho*-iodination followed by *in situ* halogen dance has been carried out on 5-bromonicotinic acid (**2.133**) using an unusual base (Scheme 2.27).[98] An interesting application of the halogen dance in total synthesis is the one-pot reaction sequence that led in excellent overall yield to a close precursor of the alkaloid amphimedine (**2.135**→**2.137**, Scheme 2.27).[99] Although much remains to be learned about the mechanistic details of this reaction, experimental evidence supports the hypothesis of an intermolecular mechanism based on two consecutive lithium–halogen exchange steps that are thermodynamically driven (Scheme 2.28). All halogen dance reactions can be explained through the intermediacy of key polyhalogenated species like **2.142** (defined as cocatalysts) which, in many cases, have been isolated.[100] The *ortho* metalation of iodopyridines may benefit from the use of

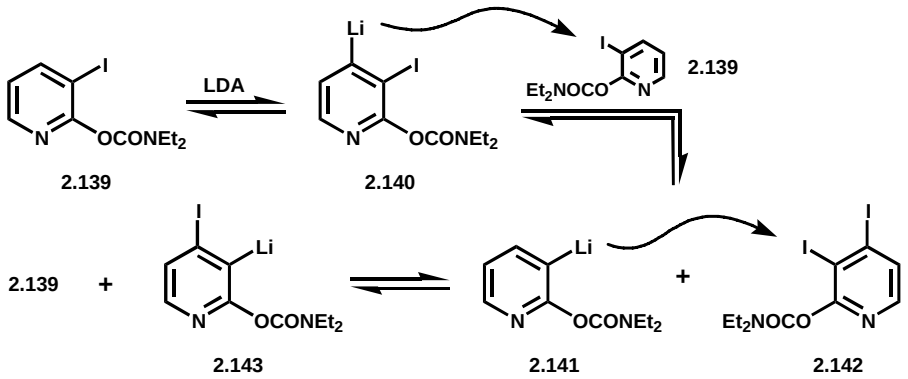
lithium metal complexes[101] and mixed Mg/Li bases[102] whose *ortho*-lithiated products can be reasonably expected to display a lower tendency towards dehydrohalogenation and undesired halogen-dance.



Scheme 2.26



Scheme 2.27

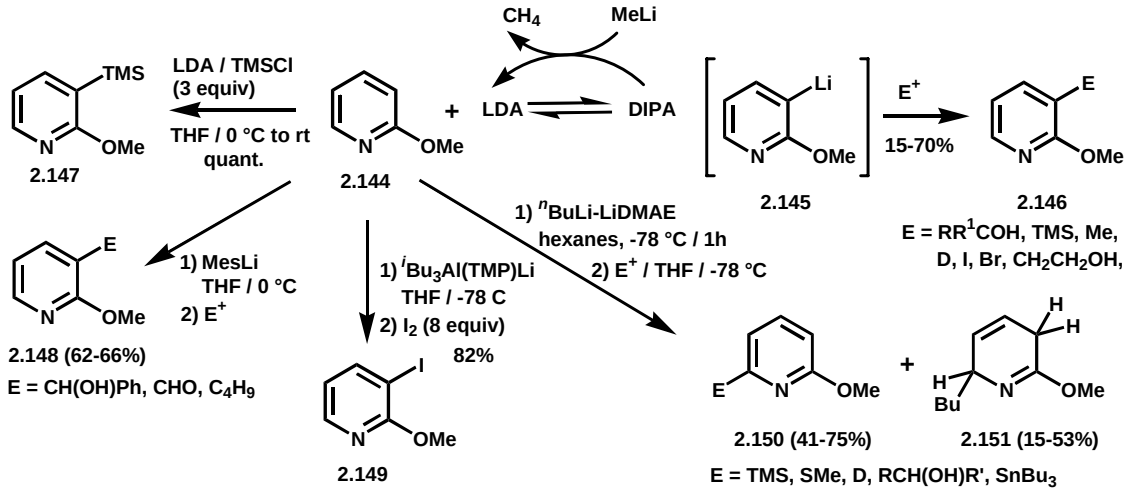


Scheme 2.28

2.2.2. Oxygen-based DMGs

Paralleling the behaviour of 2-halopyridine and despite its inherent richer π system, 2-methoxypyridine is more prone than its 3- and 4-regioisomers to nucleophilic addition of ^{n}BuLi at −78 °C, perhaps due to intial RLi N-coordiation. Even the less nucleophilic ^{n}BuLi/LiDMAE system did not display high chemoselectivity[103] (**2.150** + **2.151**, Scheme 2.29) and neither has any result with the $TMSCH_2Li$/LiDMAE aggregate been reported to date. LDA predictably fails to achieve complete deprotonation of 2-methoxypyridine[104]

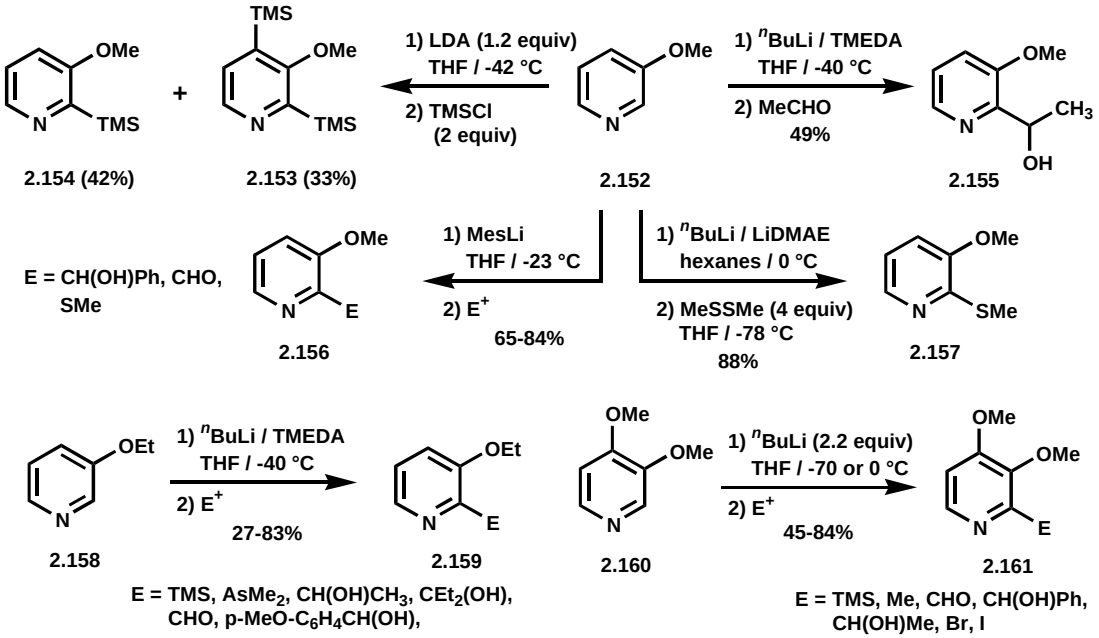
unless the equilibrium shift technique (simultaneous addition of an excess of base and TMSCl) is used, which finds, however, a heavy limitation in the small number of base-compatible electrophiles which are available (**2.144** → **2.147**).[105]



Scheme 2.29

A remarkable improvement of the yields was obtained with the application of the LDA catalyzed metalation technique (**2.144** → **2.146**) although it has been now superseded by the use of mesyllithium, a hindered base that has been found by Comins to promote efficient metalation of all three isomeric methoxypyridines (**2.148**).[106] Finally, iodination of 2-methoxypyridine has been achieved with the aluminum "ate" base, $^{i}Bu_3Al(TMP)Li$, although the pyridyl aluminate intermediate has been quenched only with a large excess of iodine (**2.149**).[107] Unlike 3-halopyridines, 3-alkoxypyridines do not undergo regioselective lithiation with LDA (**2.154** and **2.153**, Scheme 2.30). However, their metalation resembles that of 3-fluoropyridine, since the 2-lithiated 3-methoxypyridine, generated selectively with ^{n}BuLi/TMEDA in THF at –40 °C, slowly isomerizes to its 4-lithio isomer with time or increase of temperature (60 °C).[108] The initial formation of the

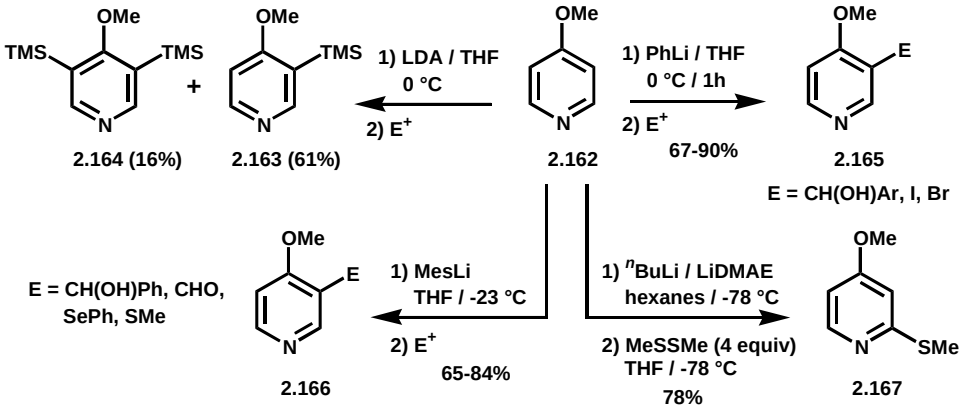
C_2-lithio species may be due to the combination of the MeO DMG effect and the chelation of ^{n}BuLi/TMEDA with the nitrogen, which effectively provides a CIPE.



Scheme 2.30

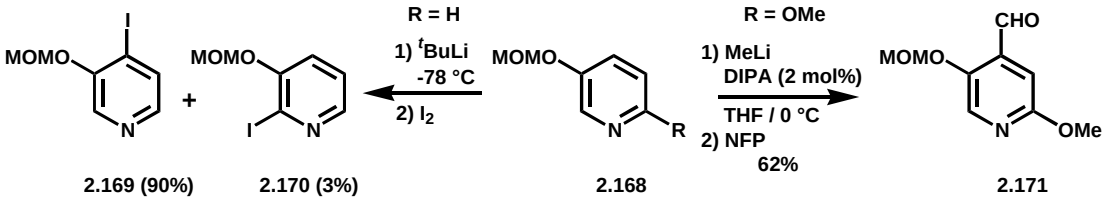
This unusual orientation pattern is not observed in the lithiation of pyridines bearing other oxygen-based DMGs (OMOM, $OCONR_2$, $OC(S)NEt_2$) at C_3. In these cases, a synergistic coordinative effect of the two heteroatoms in the DMG has been suggested to reduce the significance of the nitrogen-base interaction. However, the C_2-selective metalation of **2.152**, while easily rationalizable in the reaction with LiDMAE (**2.152** → **2.157**), is difficult to explain when the reaction is carried out in the absence of any additive amine (**2.158** → **2.159** and **2.160** → **2.161**,[59c] Scheme 2.30) and suggests that the role of TMEDA may not be critical. As with the other isomers, 4-methoxypyridine is metalated with poor regioselectivity through an unfavourable equilibrium which restricts electrophilic quench to silicon (**2.163** + **2.164**, Scheme 2.31).[106,109] While the C_3-lithiation of this substrate relies on mesyllithium (**2.166**), and, at a higher temperature, on

phenyllithium (**2.165**),[59c] C_2-functionalization is achievable with ^{n}BuLi/LiDMAE; however, the latter reaction has not been generalized with respect to electrophiles (**2.167**).



Scheme 2.31

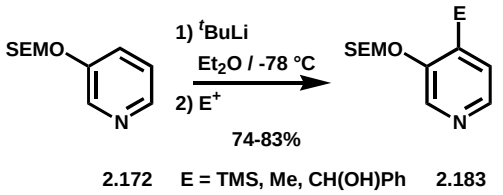
Among the MOM-derived pyridinols, only the 3-isomer has been subjected to D*o*M and without systematic scope exploration. ^{t}BuLi was found to effect metalatation of this substrate with a large predominance of C_4-regioselectivity as shown by iodine quench experiments (**2.169** and **2.170**, Scheme 2.32).[110]



Scheme 2.32

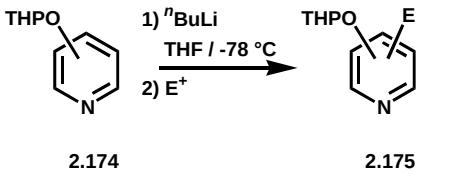
The OSEM and, recently, the OTHP group have also displayed good DMG properties in D*o*M reactions of pyridines. 3-OSEM-pyridine (**2.172**) was shown to undergo C_4-lithiation with ^{t}BuLi at –78 °C, while 2-lithiation was smoothly achieved under the same conditions after TMS-protection of the 4-position (Scheme 2.33).[111] Standard

regioselectivity has been observed for the metalation of pyridines bearing the OTHP group whose power as DMG, through an intermolecular competition experiment, was shown to be between that of the MeO and the carbamate group[112] (Scheme 2.34).



2.172 E = TMS, Me, CH(OH)Ph 2.183

Scheme 2.33



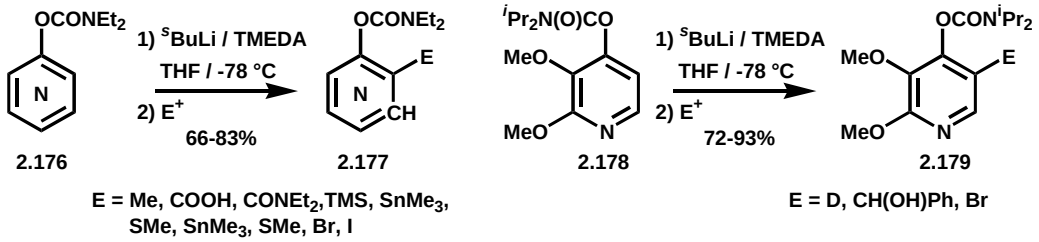
2.174 2.175

3-OTHP 4-E = CH(OH)-p-MeOC$_6$H$_4$, Me, D, I, SPh, CHO (65-96%)

4-OTHP 3-E = D, I, CH(OH)-p-MeOC$_6$H$_4$ (50-92%)

Scheme 2.34

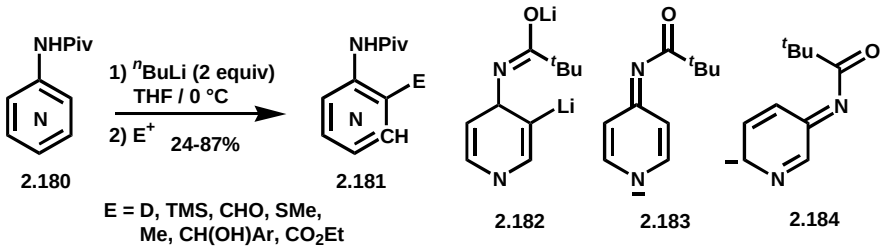
While only the 3-isomer of the *O*-pyridyl thiocarbamates undergoes selective lithiation at C_4,[113] the powerful *N*,*N*-diethylcarbamate group, at the top of the DMG hierarchy, has displayed excellent performance in all three pyridyl isomers with exclusive C_4-lithiation of the 3-pyridyl *O*-carbamate (Scheme 2.35).[114] Although the deprotonative equilibrium observed with LDA is sufficient to allow silylation of pyridylcarbamates owing to the *in situ* base-electrophile compatibility effect, their complete lithiation requires ^{s}BuLi/TMEDA and low temperatures to prevent the facile anionic *ortho*-Fries rearrangement. Both pyridyl *O*-carbamates[115] and pyridyl *O*-thiocarbamates[116] have been subjected to cross coupling reactions although the latter methodology requires further definition of scope and limitations. During the synthesis of aptenin B, Quéguiner has observed the unusual cleavage of the diethylcarbamate group presumably resulting from ^{s}BuLi attack. To overcome this difficulty, DMG replacement with the bulkier diisopropyl-*O*-carbamate was carried out and led to the desired 5-substituted compounds **2.179**.[59b]



Scheme 2.35

2.2.3. Nitrogen-based DMGs

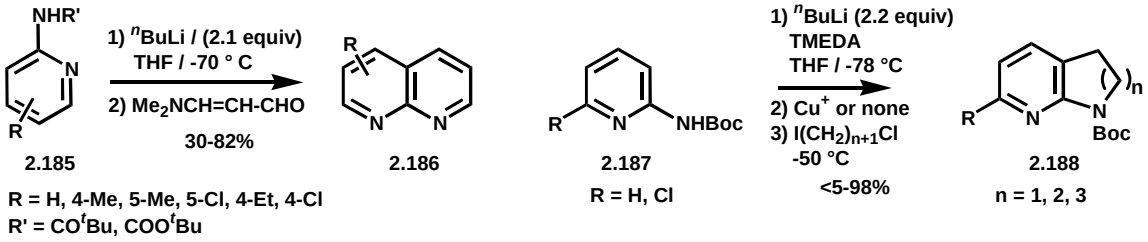
Quéguiner[117a] and Storr[118] singled out two nitrogen-based DMGs (NHCO^{t}Bu, NHCOO^{t}Bu respectively) for D*o*M application in the pyridine series. The 2- and 4-*N*-(pivaloyl)aminopyridines **2.180** were lithiated at 0 °C and their dianions (*e.g.* **2.182**) were trapped with electrophiles without observation of undue and not unexpected alkyllithium addition to the pyridine ring (Scheme 2.36).



Scheme 2.36

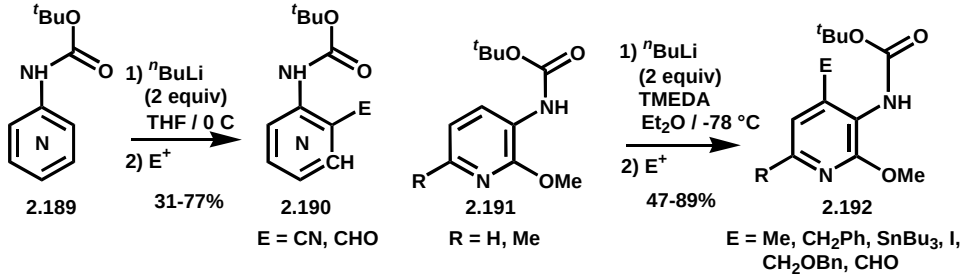
Resonance structures of the monolithiated show that, unlike its 2- and 4-isomer (*e.g.* **2.183)**, the monolithiated 3-*N*-(pivaloyl)aminopyridine **2.184** cannot place a negative charge on the ring nitrogen and reduce the electrophilicity of the C=N. In fact, competitive nucleophilic addition of ^{n}BuLi to the 4-position of 3-*N*-(pivaloyl)aminopyridine accounts for ~ 40% of the product mixture. Through an adaptation of Muchowski's approach to quinolines,[119] both the NHCO^{t}Bu and NHBoc groups have been recently used in a one-pot synthesis of 1,8-naphthyridines **2.186**

(Scheme 2.37).[120] In a similar one-pot annulation protocol, 2-*N*-(Boc)aminopyridines **2.187** were converted into the bicylic products **2.188** by treatment of their *o*-lithiated derivatives with α,ω-dihaloalkanes followed by *in situ* cyclization.[121]



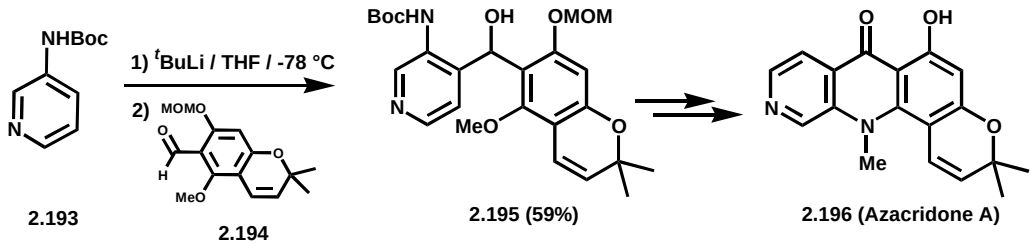
Scheme 2.37

An intermolecular competition experiment has shown that, in the pyridine series, the NHBoc group is a much weaker DMG compared to the NHCO^{t}Bu group (<5% : >95%); however, despite the lack of systematic exploration[122] in the D*o*M of pyridines, the use of the NHBoc is often preferred to the NHCO^{t}Bu group because of its higher hydrolytic lability (Scheme 2.38).



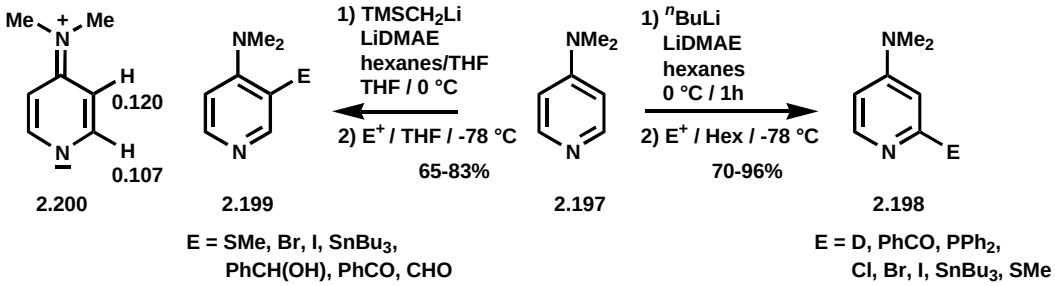
Scheme 2.38

For instance, Kelly has recently used the NHBoc DMG in the first total synthesis of the alkaloid azacridone A (**2.196**, Scheme 2.39).[123]



Scheme 2.39

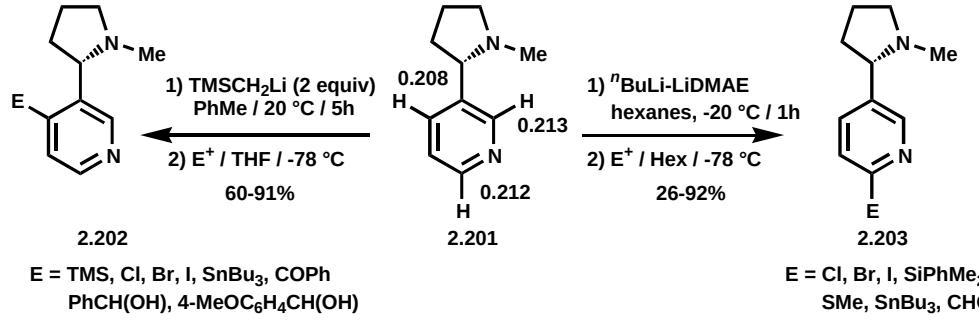
The dialkylamino, arylamino and amino groups have not gained prominence in aromatic D*o*M as DMGs possibly due to the *N*-lone pair delocalization that subdues the coordination with the metalating agents.[124] However, DMAP (**2.197**) has been metalated both at C_2, by applying the usual condition for anchorage of the base to the ring nitrogen (**2.198**),[125] and at C_3 by preventing that chelate from forming through the addition of THF, a strongly coordinating solvent (**2.199**, Scheme 2.40).[126] PM3 charge calculations show, as suggested by resonance structure **2.200**, that the dimethylamino group depresses the acidity of H_2 and, accordingly, the C_3 deprotonation of **2.199** under these conditions is a selective process.



Scheme 2.40

2.2.4. Carbon-based DMGs

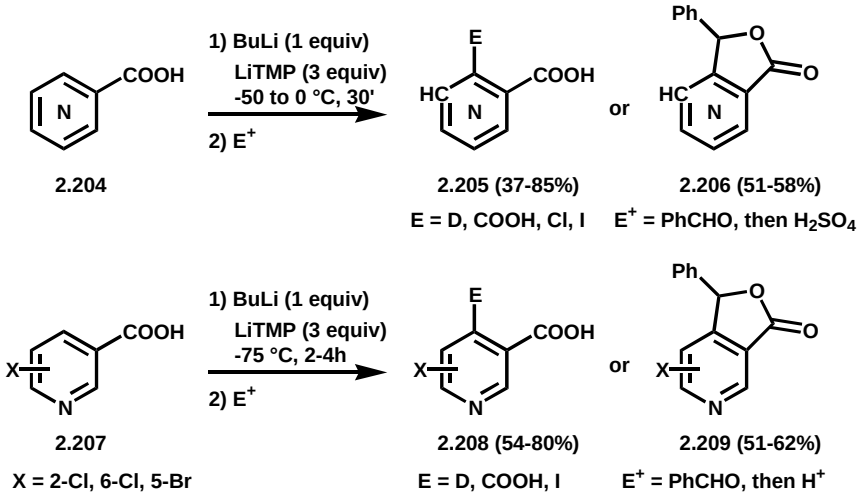
Carbon-based DMGs for which *ortho*-lithiation conditions have been established in the pyridine series include carboxylic acids, amides, oxazolines, nitriles and *in situ* derived α-aminoalkoxides. All 3-DMG-pyridines of this group, including (*S*)-nicotinine (**2.201**), underwent lithiation following the more common C_4-regioselectivity. Although $(CH_2)_nNR_2$ groups are considered very poor DMGs, some chelating effect of the pyrrolidine nitrogen must be invoked to explain the abstraction of the least acidic proton H_4 (according to PM3 proton charge calculations) in the selective lithiation of (*S*)-nicotine with $TMSCH_2Li$ (**2.202**, Scheme 2.41).[127] While LiDMAE has no effect on the regioselectivity of the latter reaction, it promotes C_6-selective metalation (**2.203**) when used with ^{n}BuLi at –20 °C, the argument being that the C_2 position is too crowded to accommodate the large chelate **2.88** (Fig. 2.2).[128] The C_2-position could be selectivily metalated using LiTMP but is limited to functionalization only with *in situ* electrophiles (TMSCl, Cy_3SnCl, 64-94%). C_6-Chlorination of (*S*)-nicotine is the first of six steps in Comins' total synthesis of (*S*)-brevicoline (17% overall yield).[129]



Scheme 2.41

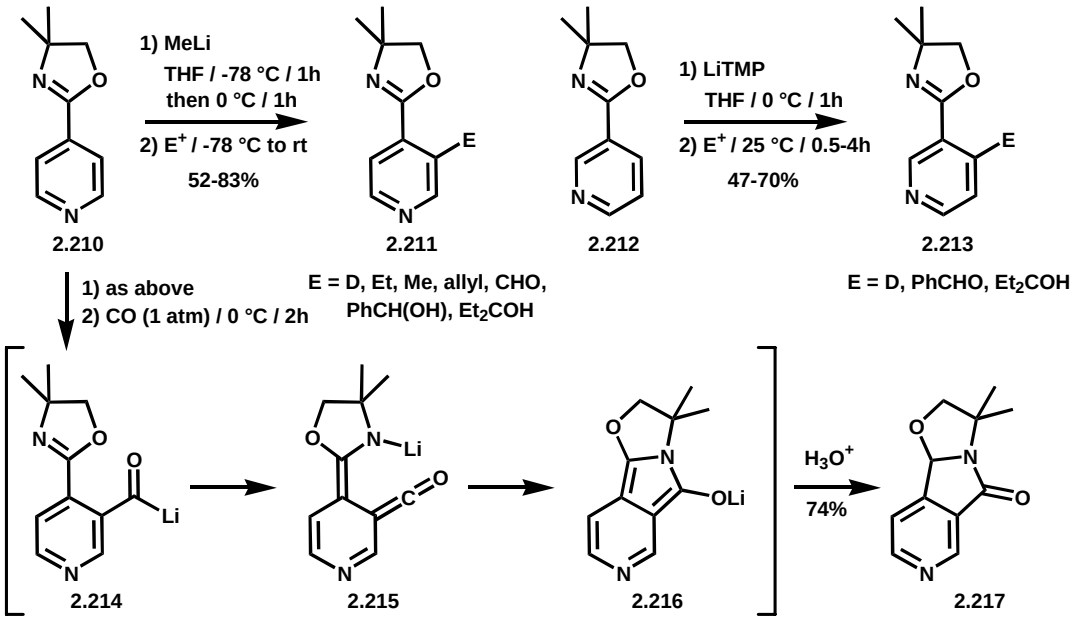
Pyridine carboxylates, obtained *in situ* by the addition of one equivalent of ^{n}BuLi to the carboxylic acids **2.204** and **2.207**, may be metalated efficiently with an excess of LiTMP

as evidenced by the incorporation of high percentages of deuteration upon quench with D_2O (Scheme 2.42).[130,98] However, although ^1H NMR of the crude samples showed that lithium carboxylates were the only pyridinic compounds, the difficult isolation of the free acids led to considerable erosion of the yields.



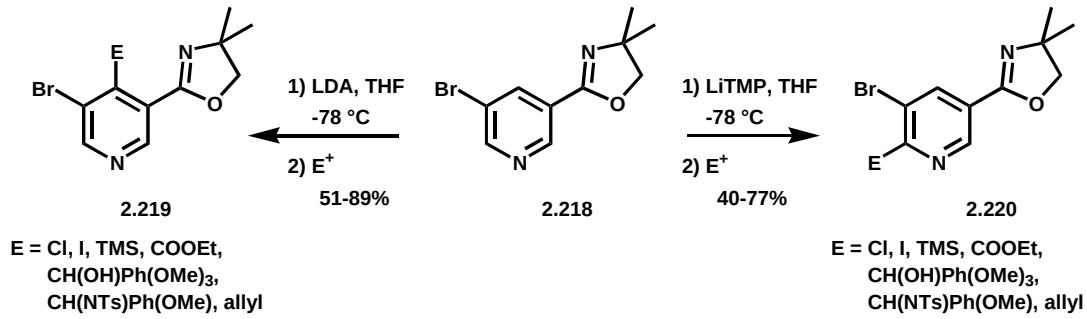
Scheme 2.42

Detailed studies have demonstrated the facile nucleophilic addition of alkyl and aryllithiums to oxazolinylpyridines which, in some cases are highly selective and therefore synthetically useful.[131] On the contrary, *ortho*-metalation of these substrates has been only briefly explored by Meyers in 1978. While LDA is inefficient in the D*o*M of these systems, LiTMP[132] and MeLi[133] were used successfully on 3- and 4-pyridyloxazolines **2.212** and **2.210**, respectively, although the range of tested electrophiles was limited (Scheme 2.43).



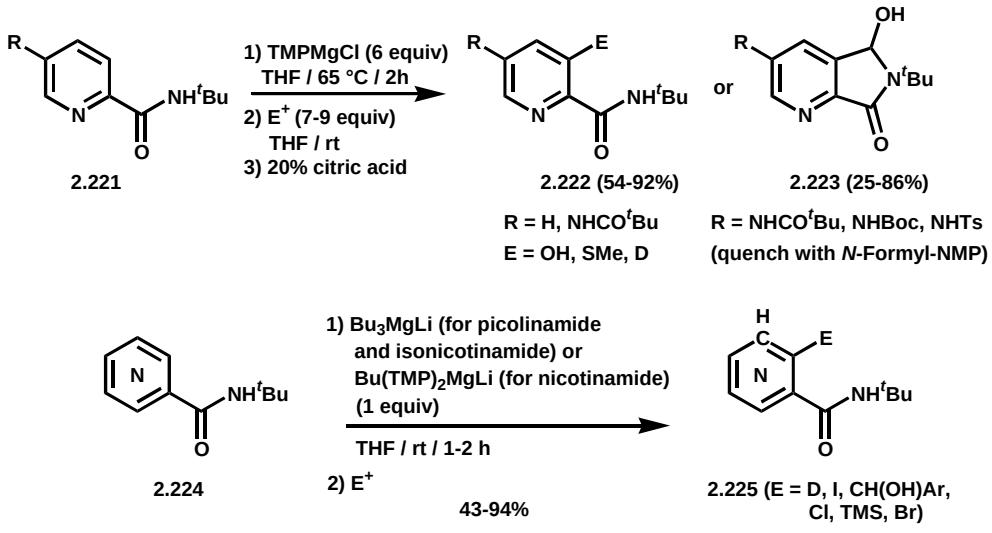
Scheme 2.43

More recently, Murai has reported a carbonylative cyclization which involves the nicotinoyllithium intermediate obtained from D*o*M/CO quench of **2.210,** isomerisation and cyclization to afford the tricyclic compound **2.217** in good yield (Scheme 2.43).[134] Furthermore, the optionally site selective metalation of **2.218** has been recently developed through the proper choice of the base (Scheme 2.44). While PhLi undergoes addition to C_4 in high yield,[135] the harder bases LDA and LiTMP can selectively effect C_4 and the C_2 lithiation, respectively, to **2.219** and **2.220**.[136] In a well known scenario, (3-fluoropyridine and 3-methoxypyridine, Schemes 2.20 and 2.30, respectively), the 2-lithio derivative of **2.218** obtained with LiTMP was shown, through D_2O quench at different temperatures, to slowly equilibrate at −50 °C with the more thermodynamically stable 4-lithio isomer.



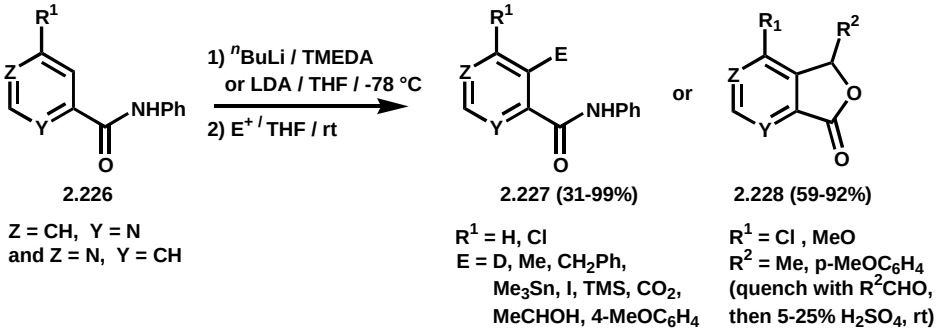
Scheme 2.44

Studies by Epsztajn and Mulzer concerning the metalation of pyridine systems has singled out two strong DMGs (CONHPh and CONH^{t}Bu respectively) among the secondary pyridine carboxamides (Scheme 2.45). Mulzer found that, although **2.221** can be metalated using ^{n}BuLi, TMPMgCl often affords comparable or higher yields.[137] However, a large excess of the electrophiles and of the costly base is required as well as relatively high temperatures. Quéguiner has recently improved the magnesiation of pyridine carboxamides (especially *N*-^{t}butyl pyridine carboxamides) with particular regard to the reaction conditions which allow regioselective metalation of the substrate at rt and without excess of base (**2.224** → **2.225**, Scheme 2.45).[138]



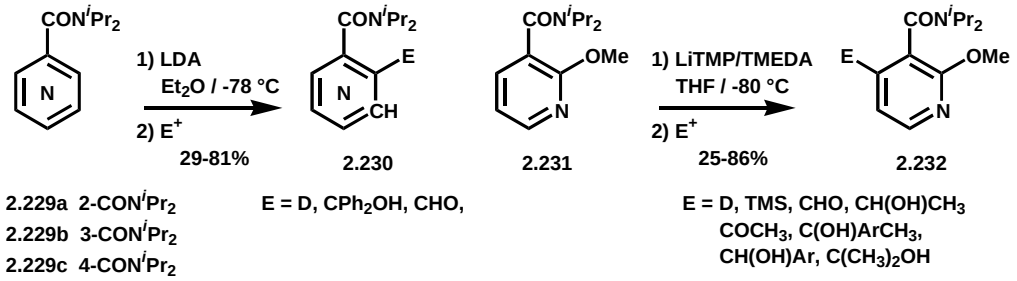
Scheme 2.45

As for the lithiation of *N*-phenyl pyridinecarboxamides, Epsztajn's work has revealed a different behaviour in one of their three possible pyridine isomers.[139] While picolinaldehyde and isonicotinanilide **2.226** were metalated smoothly using ^{n}BuLi, the corresponding nicotinic isomer was shown to be nucleophilically attacked by MeLi, BuLi and PhLi to furnish 1,4-adducts (Scheme 2.46).



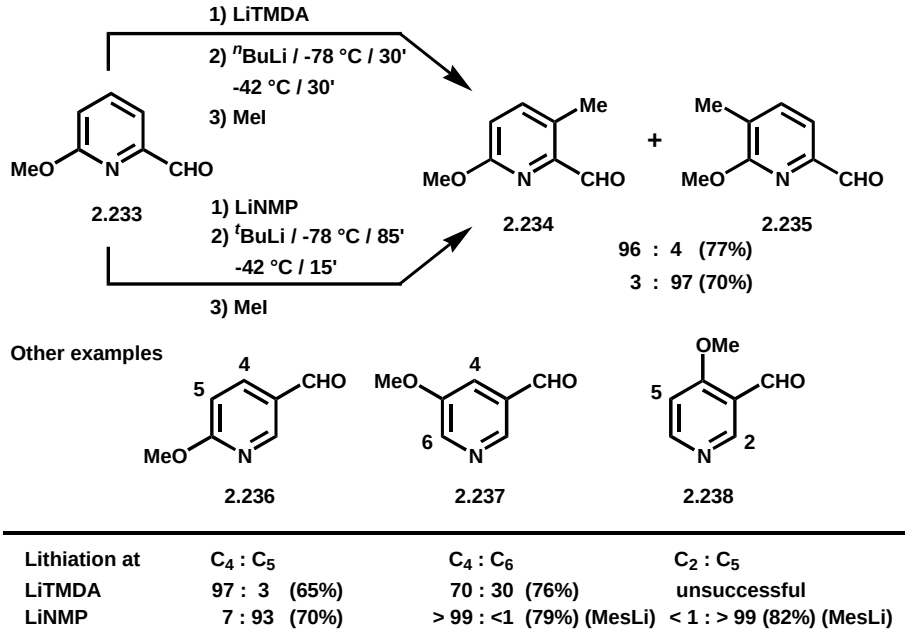
Scheme 2.46

Exploration of the tertiary amides $CONMe_2$, $CONEt_2$ and $CON^{i}Pr_2$ groups in metalation of pyridine systems has shown that, while nucleophilic addition to the ring is not an issue even with alkyllithium reagents,[97,140] the undesired addition to the DMG must be addressed using low temperatures, short reaction times and bulky lithium amides. Epsztajn showed that, when treated with Et_2NLi, dimethyl pyridine carboxamides undergo transamidation and little *ortho* metalation as evidenced by quench with D_2O and acetophenone.[141a] A limited number of electrophiles could be introduced in modest yields by subjecting *N,N*-diisopropyl pyridine carboxamides to reaction with LDA[141a] or LiTMP[141b-c] (Scheme 2.47) followed by quenching experiments whereas, for their *N,N*-diethyl analogues, rapid self-condensation was demonstrated to be a concurrent when not a predominant process.[141a-b] The D*o*M of pyridinecarboxamides is discussed in detail in the following section.



Scheme 2.47

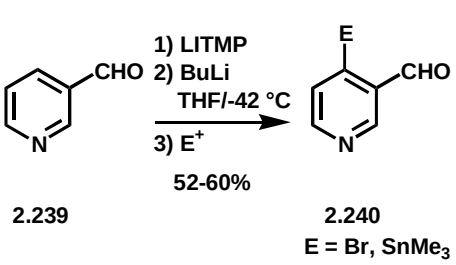
The use of α-aminoalkoxides as DMGs, championed by Comins,[142] has found a versatile application in the *ortho*-metalation of various isomeric methoxypyridinecarboxaldehydes (**2.233**, **2.236**-**2.238**) where a generally high degree of regioselective control was obtained simply by changing the amine component of the DMG (Scheme 2.48).[143]



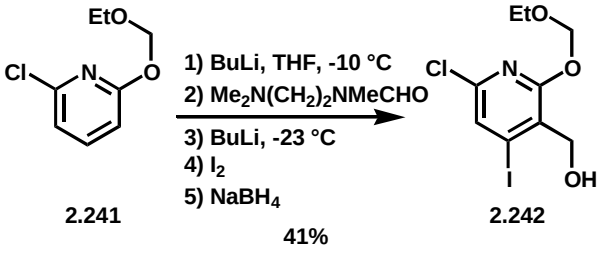
Scheme 2.48

Both lithium *N,N,N*'-trimethylethylenediamide (LiTMDA) and lithium *N*-methylpiperazide (LNMP) protected the formyl group from attack of the base but only the former was shown to be an efficient directing group. While Comins' systematic

studies applied MeI as the only quenching electrophile, Br, $SnMe_3$ and I (the latter in one pot) groups have been introduced in studies which led to the short total syntheses of schumanniophytine (Scheme 2.49)[144] and (*S*)-camptothecin (Scheme 2.50).[145]



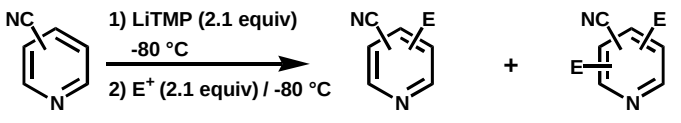
Scheme 2.49



Scheme 2.50

Rault's recent work concerning the D*o*M of cyanopyridines[146] with LiTMP is conceptually similar to Comins' methodology. Of the two equivalents of base required, one is suggested to reversibly add to the cyano group, while the second effects the *ortho*-deprotonation (Table 2.4). However, the excess of base often leads to double iodination and silylation with lower yields of the desired product **2.244**. Kristensen has independently applied these conditions to the synthesis of all three isomeric cyanopyridyl boronic acids whose neopentylglycol esters were formed *in situ*.[147] Despite the use of lower excess of the base/$B(OPr)_3$ (1.2/1.4 equiv), Kristensen obtained much higher yields of product (52-94%), which points the finger to the daunting isolation of pyridylboronic acids.

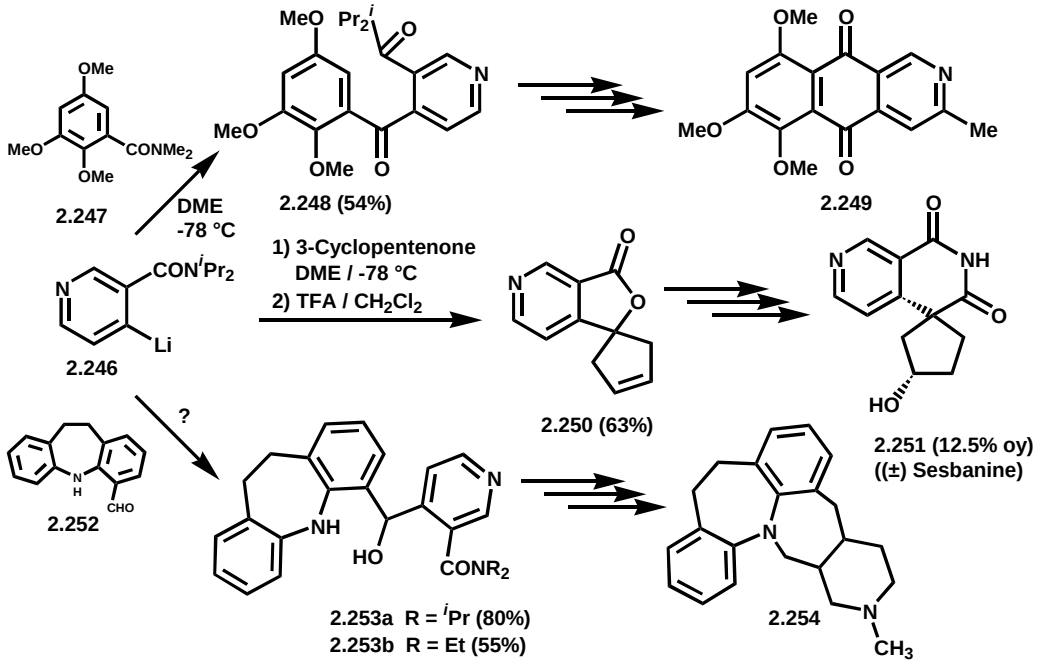
Table 2.4 D*o*M of Cyanopyridines



4-CN	C_3-E = I, TMS Br, Cl, $B(OH)_2$ COOH (41-75%)	$C_{3,5}$-E = I, TMS (14, 17%)
3-CN	C_4-E = I, Cl, $B(OH)_2$ (37-56%)	$C_{2,4}$-E = I (17%) C_2-E = Cl (7%)
2-CN	C_3-E = I, Cl, $B(OH)_2$ (52- 75%)	$C_{3,6}$-E = I (19%)

2.2.5. D*o*M of Pyridyl Carboxamides

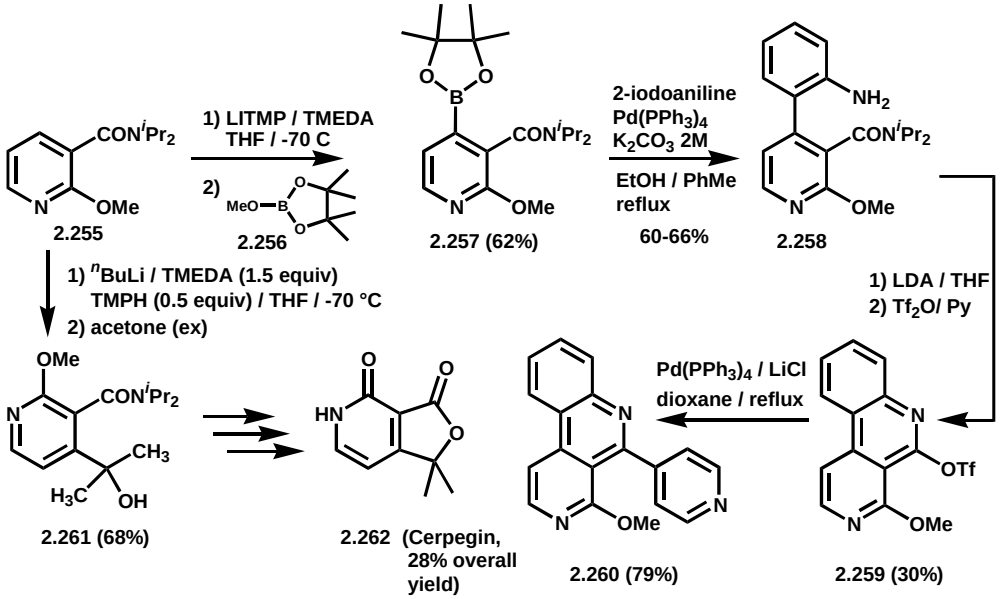
Following the deep mark that the tertiary amide group has impressed on the development of D*o*M of aromatic compounds,[148] tertiary pyridine carboxamides have often been lithiated within synthetic routes towards natural products. The diisopropylamide DMG, in particular, has been preferred to its smaller diethylamide analogue, because it does not easily undergo nucleophilic attack by lithiated species (be these a generated pyridyllithium intermediate or an RLi reagent) to form ketones.[141a] Thus, the *ortho*-lithiated diisopropylnicotinamide **2.246** was used at the onset of the total syntheses of both the antibiotic bostrycoidin[141c] and the cytotoxic alkaloid sesbanine **2.251**[141b] by Watanabe and Iwao respectively (Scheme 2.51).



Scheme 2.51

In Watanabe's work, **2.246** was condensed with the trimethoxybenzamide **2.247** (synthesized by D*o*M) to obtain ketone **2.248** which, in a number of steps, was converted into the 2-azaanthraquinone **2.249**, a known dimethylated precursor of the target

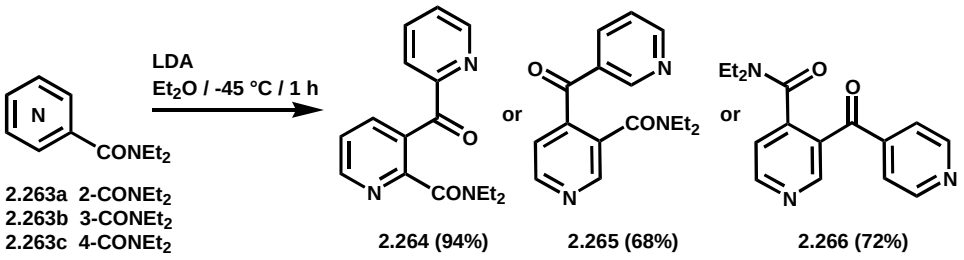
molecule. In Iwao's work, **2.246** was quenched with 3-cyclopentenone and the crude alcohol obtained, without isolation, was lactonized to **2.250** in reasonable yield without isolation. Further manipulation of the latter diastereoselectively led to (±) sesbanine (**2.251**) in 12.5% overall yield. During the synthesis of the rigid imipramin analogue **2.254**, **2.246** was condensed with the dibenzazepine **2.252** which, through stepwise but exhaustive reduction of all non benzenic moieties, led to a *cis/trans* mixture of the target molecule.[149] Quéguiner has resorted to the metalation of the 2-methoxy nicotinamide **2.255** in the attempted total syntheses of the alkaloids cerpegin[141d] and amphimedine (Scheme 2.52).



Scheme 2.52

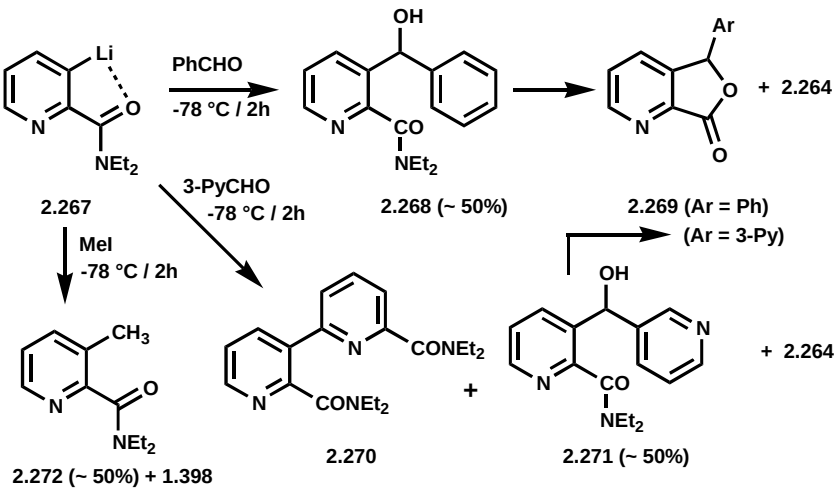
In the first work, 4-lithiated **2.255** was quenched with acetone and further acid-catalyzed manipulation of the alcohol **2.261** furnished the target **2.262** in 28% overall yield. In the more complex synthesis of amphimedine, **2.255** was subjected to a typical D*o*M-boronation-cross coupling sequence; however, anionic cyclization of the phenylpyridine

2.258 was disappointing and, although the feasibility of the method was proven, the authors were forced to explore alternative routes. Epsztajn was the first to show that self-condensation is a serious problem when metalating diethylpyridine carboxamides **2.263** (Scheme 2.53) due to the propensity of the resulting lithiated species to undergo instantaneous condensation with starting material or with another *o*-lithiated species to form ketones **2.264-2.266**.[141a] The occurrence of this process may explain the lower yields that Iwao and Martin reported when attempting to prepare **2.250** and **2.253**, respectively, from diethylnicotinamide (Scheme 2.51).



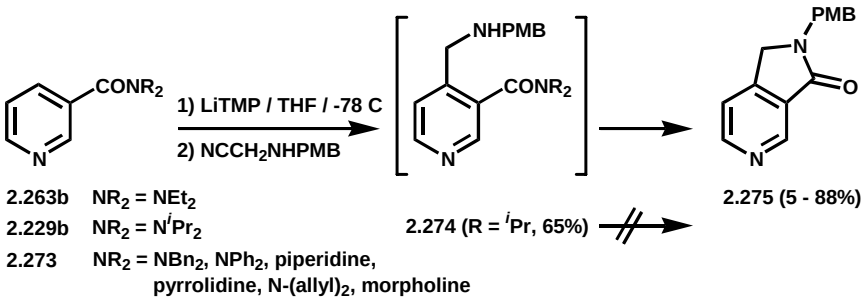
Scheme 2.53

In a more recent attempt, Avendaño showed that diethyl picolinamide (**2.263a**) could be *ortho*-functionalized with an external electrophile if its metalation with ^{s}BuLi was immediately followed by addition of the electrophile (Scheme 2.54). Due to the instability of the products **2.268**, **2.271** and **2.272**, the yield was indirectly estimated (^{1}H NMR on the crude material) as ~ 50%, the remainder being products of unpreventable condensation (**2.264**) and dimerization processes (**2.270**). If the $CONEt_2$ DMG may appear of little synthetic utility in the metalation of the pyridine series, the use of the more bulky $CON^{i}Pr_2$ has its own drawbacks in its lower pliability, which inevitably reflects on its synthetic applicability.



Scheme 2.54

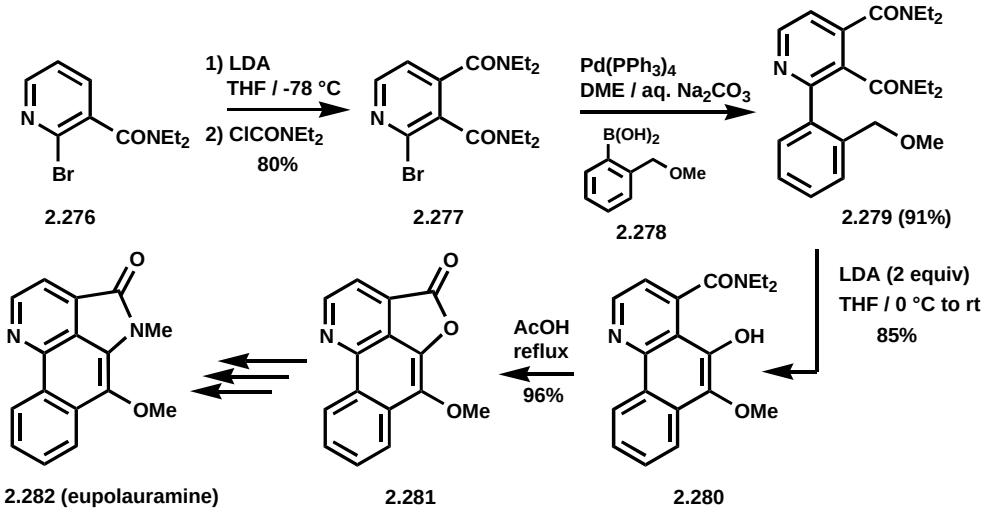
To use a recent example, Marsais' optimization of an aminomethylation-cyclization tandem reaction reveals that, while *N*,*N*-diethylnicotinamide gives the product **2.275** in 54% yield, the corresponding diisopropylamide **2.229b** is too hindered to undergo the corresponding cyclization (Scheme 2.55).[150] The authors found that a good compromise was the use of the piperidylcarboxamide group which, despite its being a "tied back" version of the $CONEt_2$ group, was proven capable of avoiding self-condensation and, at the same time, inadequate to prevent the ring closing step to the desired product **2.275**.



Scheme 2.55

The conversion (**2.274** → **2.275**) closely resembles the desired cyclization of **2.258** (Scheme 2.52) which, it could be argued, may have given a better outcome if the less

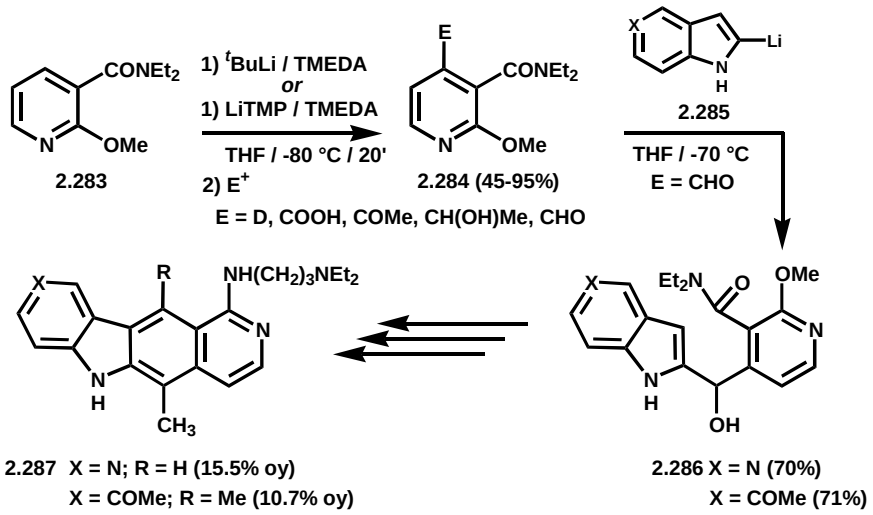
hindered diethylamide group had been used. As a matter of fact, the bulky $CON^{i}Pr_2$ group is not a stringent requirement for the metalation of **2.255** (Scheme 2.52), because substituted diethyl pyridinecarboxamides appear to be more stable towards self-condensation. To illustrate, in the total synthesis of the alkaloid eupolauramine accomplished in our group by Wang,[151] diethyl 2-bromonicotinamide (**2.276**) was carbamoylated under standard metalation conditions to give **2.277** in 80% yield (Scheme 2.56). Then, cross coupling of **2.277** furnished azabiaryl **2.279** which, through admirable pliability of the diethylamide group, led to the lactone **2.281**, a key intermediate towards the target alkaloid **2.282**.



Scheme 2.56

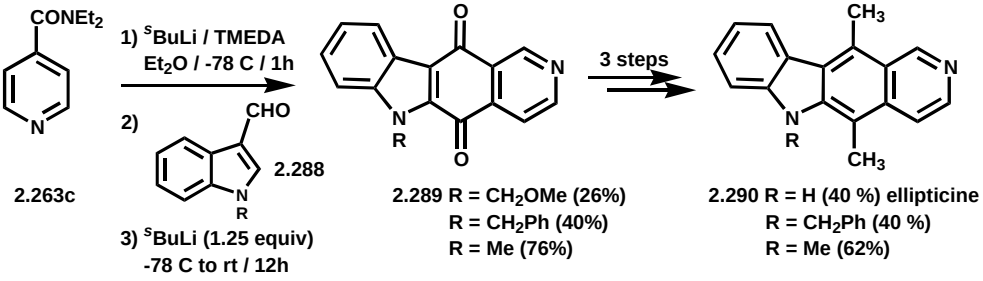
Similarly, during the total synthesis of two modified ellipticines, Dormoy and Heymes studied the metalation of both **2.283** and its diisopropyl homologue (Scheme 2.57).[141e] Although a case-to-case comparison with the boronation of **2.255** (Scheme 2.52) cannot be made, the diethylamide **2.283** was found to provide the expected products in remarkable yields. The robust procedure was then used to prepare the formylated

intermediate **2.284** which was condensed with the indole and azaindole **2.286** in 70% yield towards the preparation of ellipticine derivatives **2.287**.



Scheme 2.57

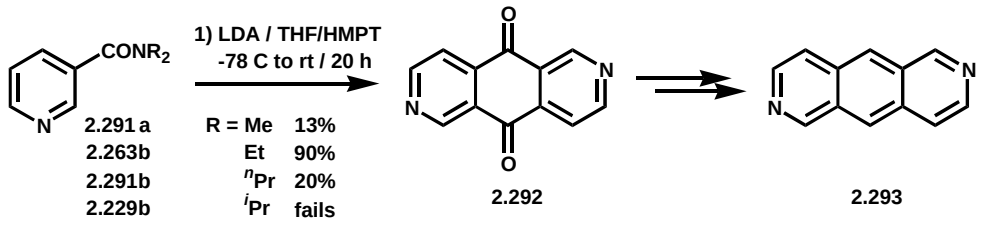
Among the numerous examples of post-D*o*M $CONEt_2$ manipulation, Snieckus has shown that intermediates similar to **2.286** can be modified *in situ* through a second metalation leading to diheterocyclic benzoquinones **2.289** which are valuable intermediates in the synthesis of ellipticines **2.290** (Scheme 2.58).



Scheme 2.58

A similar tandem D*o*M was applied by Falck to the synthesis of pyridoisoquinoline **2.293** from nicotinamide **2.263b** (or isonicotinamide **2.263c**) with similar yields (Scheme 2.59).[152] With the exception of dimethylnicotinamide **2.291a** which, according to

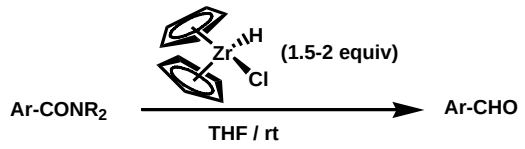
Epsztajn's results,[141a] is likely transamidated to the corresponding diisopropylamide, the correlation between the size of the DMG and the yield of **2.292** clearly points to the importance of size in facilitating condensation reactions of amide derivatives.

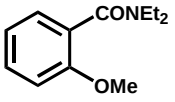
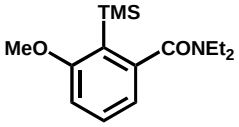
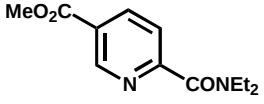
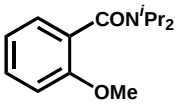
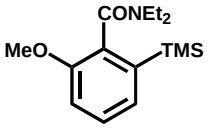
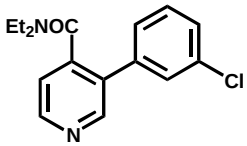
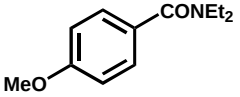
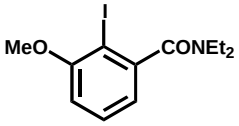
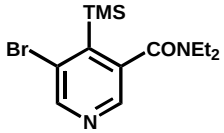
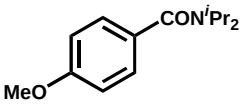
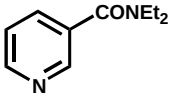
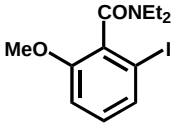
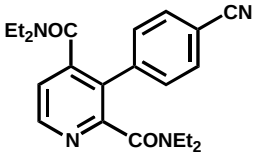


Scheme 2.59

The impressive impact that the $CONEt_2$ group has had in D*o*M-based chemistry of aromatic compounds is an obvious incentive for the investigation of its potential in the pyridine series as well. Recently, following a publication by Georg reporting the ability of the Schwartz reagent ($Cp_2Zr(H)Cl$) to reduce tertiary amides to aldehydes,[153] the Snieckus group has begun a thorough study of the scope of this protocol which focuses on the reduction of *ortho* and bis(*ortho*)substituted diethyl benzamides and heteroaryl carboxamides (Table 2.5). These results portray the profile of a very mild (rt), rapid (9 min - 2h) and selective reducing reagent which, provided limited excess is used, will not reduce the $OCONEt_2$, NHBoc, OSO_2NEt_2, OTf, COOMe, CN, $OP(O)(NEt_2)_2$, NO_2 substituents of a diethyl benzamide.[154] The lower yields sometimes obtained with 2,6-disubstituted benzamides suggests that the reaction suffers from steric hindrance (compare entries 7 and 9 with entry 1). While several diethyl pyridinecarboxamides have been reduced in good yield (entries 5, 10-13), no data are available on their bulkier analogs.

Table 2.5 Reduction of (Het)Aromatic Tertiary Amides with $Cp_2Zr(H)Cl$



Entry	Substrate	Entry	Substrate	Entry	Substrate
1	 2.294 (94%)	6	 2.298 (81%)	10	 2.302 (72%)
2	 2.295 (59%)	7	 2.299 (37%)	11	 2.303 (74%)
3	 2.296 (99%)	8	 2.300 (72%)	12	 2.304 (88%)
4	 2.297 (75%)				
5	 2.263b (99%)	9	 2.301 (26%)	13	 2.305 (66%)

However, the comparison of the yields in entries 1 and 2, 3 and 4, encourages further use of the less hindered diethylamide DMG whose easier reduction may be beneficial to the selectivity of this reaction when other Schwartz-sensitive groups are present.

2.2.6. Boronation of Pyridine Derivatives

Contrary to the ubiquitous applications of arylboronic acids and despite the significance of the pyridine moiety in bioactive and natural products, the development of cross coupling of pyridyl boronic acids has lingered behind, undoubtedly due to their notoriously difficult isolation. The water solubility and chemical instability of these

compounds have discouraged efforts in this area and only recently this deficiency is being addressed to exploit their FG compatibility, air stability and low toxicity.[155] To illustrate, a Scifinder search for boron-substituted pyridines returns almost 840 hits, reported for the largest part since 2001, and represented mainly (~750) by pyridylboronic acids and their esters (primarily pinacolates). Chemical suppliers have rapidly responded to this clear trend by introducing in their catalogues many stable and cross coupling derivatives of heteroarylboronic acids, with the pyridine and furan rings being the most popular frames. Approximately 290 pyridylboron derivatives are commercially available which, with the exception of a dozen entities, are pyridylboronic acids and pinacolates. Outside these classes, a small group of known borylated pyridines includes all isomers of diethyl(pyridyl)boranes[156] (**2.307**, Fig. 2.3), the 3-isomer being widely used in cross coupling reactions.[156c] The dimethyldi(2-pyridyl)borate anion (**2.308**) has been recently reported to be an effective ligand in the anionic catalyst $LPtMe_2$ used for arene C-H activation[157] while, among the bioactive molecules, several borinic cyclic and acyclic esters **2.309**-**2.310** have displayed antifungal and antibacterial activity.[158] Carboranes containing the B-I bond have been cross coupled with pyridylzinc reagents to give at least 3 isomeric pyridylcarboranes **2.306** which, despite their exotic structure, may have medical use by virtue of their ability to carry a pharmacophore to the hydrophobic pocket of a receptor.[159] Finally, compounds of structure **2.311** were obtained during failing attempts at subjecting pyridylboronic acids to the Petasis boronic Mannich reaction with glyoxylic acid.[160] Among the parent boronic acids, 2-pyridylboronic acid has been prepared *via* a lithium-halogen exchange procedure, but is reported to be highly prone to protodeboronation.

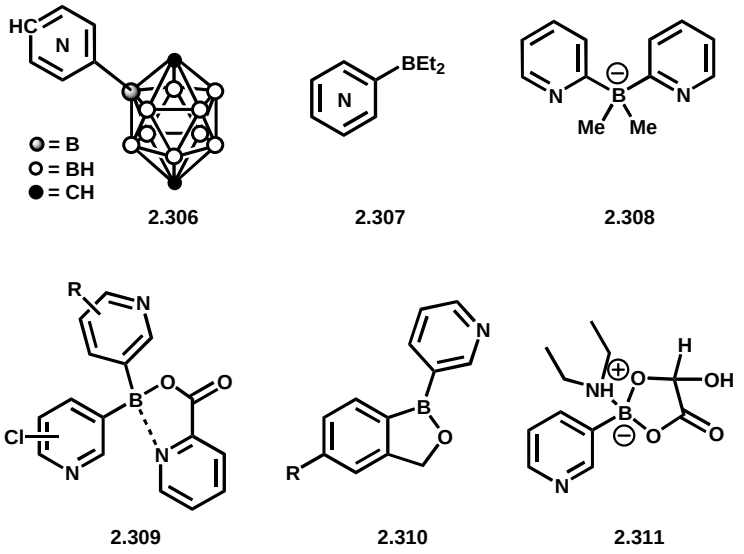
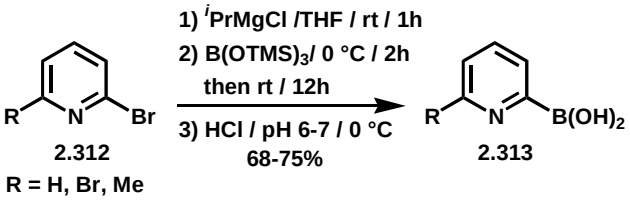


Figure 2.3 Examples of Borylated Pyridines Outside the Abundant Classes of Pyridyl Boronates and Boronic acids

To prevent this process, Hodgson and Salingue have optimized, and upscaled to kilo amounts of substrate, the direct conversion of a 2-pyridylboron "ate" complex to the more stable *N*-phenyldiethanolamine ester.[161] According to Matondo, the deboronation problem can be overcome by a careful control of the pH during the hydrolysis of the "ate" complex but, more importantly, by generating the product through treatment of pyridylmagnesium bromide with $B(OTMS)_3$ instead of a trialkylborate (Scheme 2.60).[162]



Scheme 2.60

Contrary to the other isomers, the utility of diethyl 2-pyridylborane in transition metal-catalyzed events has not been demonstrated and the dimethyl boronate has been often used as a coupling partner instead.[163] Only recently, 2-pyridylboronic acid has been

made commercially available[164] although the cross coupling yields reported so far are usually disappointing.[165] In contrast, 3-pyridyl boronic acid[166] is a relatively stable compound, and a protocol capable of generating kilogram amounts of the corresponding boroxin trimer has been described by Merck process chemists starting from 3-bromopyridine.[167] The preparation and Suzuki couplings of 3-pyridyltrifluoroborates has recently been reported.[168] 4-Pyridylboronic acid has been prepared *via* lithium-halogen exchange followed by quench with $B(O^nBu)_3$ or $B(O^iPr)_3$.[167b,169] In the domain of substituted pyridylboronic acid derivatives, systematic studies mainly by Rault[71b,78b,146a,b,170] and Bryce[171] have resulted in the preparation of shelf-stable halo pyridylboronic acids and esters in gram quantities. Figure 2.4 depicts examples of functionalized pyridylboronic acids and boronates synthesized to date by D*o*M, metal-halogen exchange, cross coupling of bis(pinacolato)diboron or pinacolborane with pyridyl bromides[172] or, in a new evolving approach, with pyridine derivatives whose C-H activation is catalyzed by an iridium catalyst.[173] The methods based on substrate lithiation emphasize careful neutralization in the work up to avoid protiodeboronation. In most of these reports, as expected, Suzuki cross coupling chemistry of the derived boronic acids or boronates was also described.

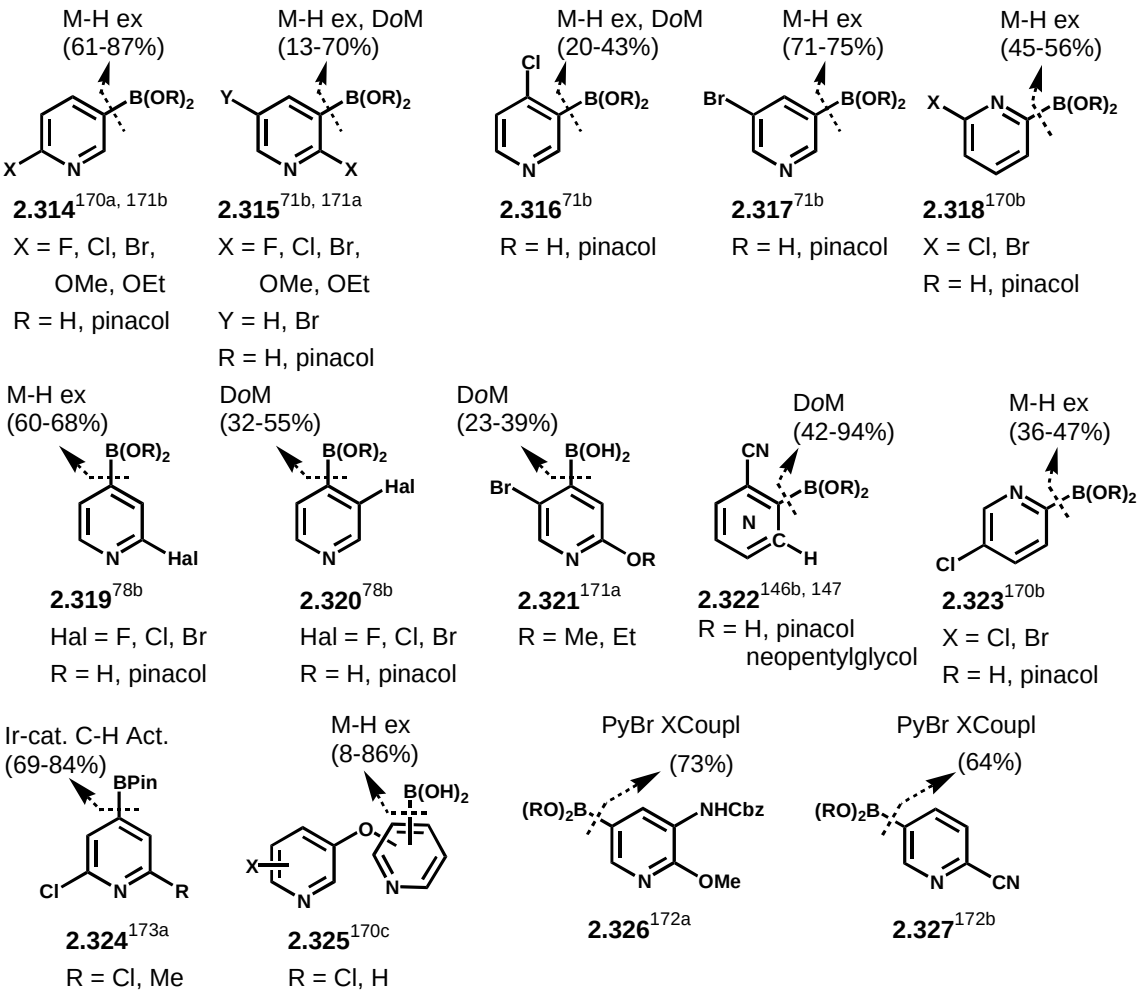
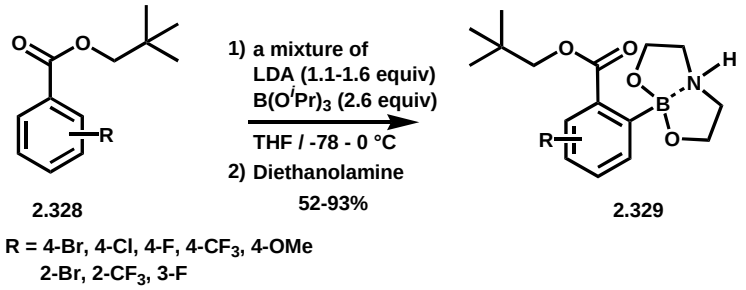


Figure 2.4 Examples of Functionalized Pyridylboronic Acids and Boronates Synthesized to Date

2.3. Aims of Research

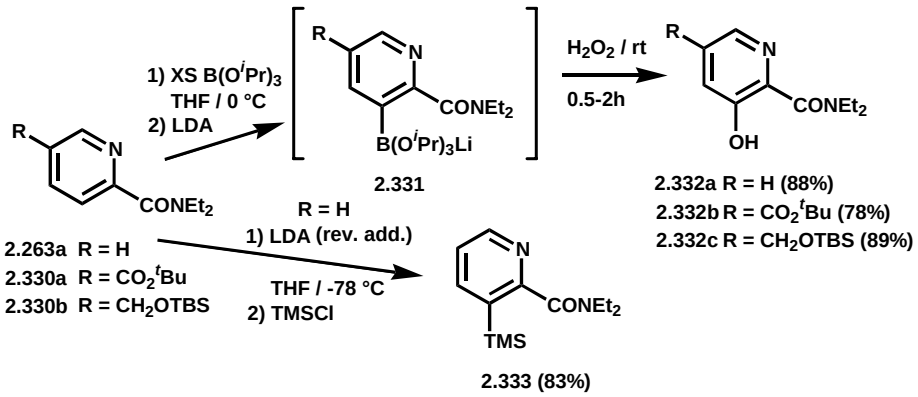
The boronation of diethylpyridine carboxamides through D*o*M, inevitably faces the limitations imposed by the self-condensation of the substrates. These competing reactions were observed by Beak during *o*-lithiation of alkyl benzoates[174] and α-lithiation of dimethylbenzamide[175] and are normally minimized by using a) low metalation temperatures (an ineffective strategy for pyridines) or b) *in situ* electrophiles. The latter, by virtue of their compatibility with certain bulky bases (generally LDA or LiTMP) with which they undergo reaction slowly, may be combined with them and this mixture

inversely added to the substrate. If the aryllithium generated undergoes reaction with the electrophile at a faster rate than addition to substrate, the reaction will be successful. Unfortunately, few electrophiles meet these kinetic requirements and even fewer are synthetically useful. Martin was the first to demonstrate the compatibility of TMSCl, $(CF_3)_2CO$ and Me_2SiCl_2 with LDA in the D*o*M of benzonitriles, isopropyl esters and diphenylsulphone,[176] while Hawkins has shown that mixtures of $B(O^iPr)_3$ with LDA are compatible and hence allow conversion of neopentyl benzoates **2.328** into the boronic ester **2.329** (Scheme 2.61).[177] The Hawkins results, yielding useful arylboronic derivatives, begged testing these conditions with diethylpyridine carboxamides.



Scheme 2.61

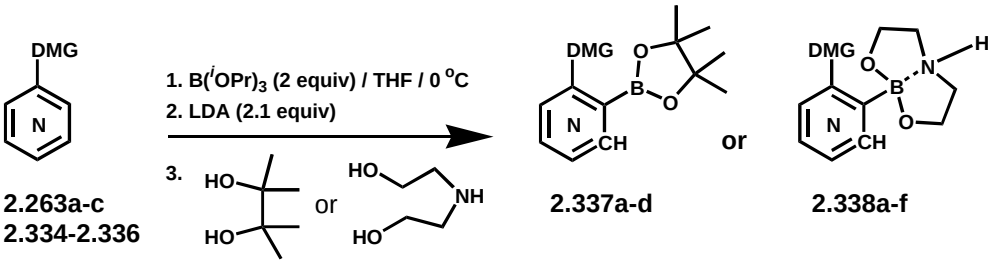
Experiments carried out in our group showed that, using TMSCl and $B(O^iPr)_3$ as *in situ* electrophiles, diethylpicolinamides **2.263a** may be silylated and boronated in high yields to give **2.332a** and **2.333** without traces of self-condensation products using TMSCl and $B(O^iPr)_3$ as *in situ* electrophiles[178] (Scheme 2.62). Through *in situ* H_2O_2 oxidation of the "ate" intermediate **2.331**,[179] this protocol was profitably applied to the preparation of two hydroxypicolinamides **2.332b,c** needed in a study towards the total synthesis of lysergic acid. These achievements prompted the development of a general method for the preparation of boronic acids of a variety of DMG-bearing pyridines.



Scheme 2.62

Initial work showed that this methodology was applicable to pyridines bearing 3-F, 3-SO_2NEt_2 and 3-$OCONEt_2$ as DMGs as well as the treacherous diethylpicolinamide, nicotinamide and isoniconicotamide.[180] However, the problematic purification of the pyridyl boronic acids, formed upon hydrolysis of the boron "ate" complexes, soon appeared and therefore derivatization to boronic esters was pursued (Table 2.6). Pinacol and diethanolamine derivatives were chosen because arylboropinacolates are known to participate broadly in cross coupling reactions,[181] while boroxazolidines are generally crystalline and very stable high melting solids.[182] Although the purification of these boronic derivatives allowed full chemical characterization, our initial studies were frustrated by low isolated yields which seriously undermined synthetic applicability. Admittedly, Bryce's and Rault's work (Fig. 2.4) also met with similar technical problems (difficult extraction, protiodeboronation) which led to erosion of isolated yields of products.

Table 2.6 DoM-*in Situ* Boronation of DMG-Bearing Pyridine Derivatives



2.263a-c
2.334-2.336

2.337a-d

2.338a-f

Pyridine	DMG	Pinacolate or Boroxazolidine	Yield (%)[a]
2.263a	2-$CONEt_2$	3-$B(OR)_2$ **2.337a**	20
2.263a	2-$CONEt_2$	3-$B(OR)_2$ **2.338a**	40
2.263b	3-$CONEt_2$	4-$B(OR)_2$ **2.337b**	60
2.263b	3-$CONEt_2$	4-$B(OR)_2$ **2.338b**	37
2.263c	4-$CONEt_2$	3-$B(OR)_2$ **2.337c**	41
2.263c	4-$CONEt_2$	3-$B(OR)_2$ **2.338c**	59
2.334	3-F	4-$B(OR)_2$ **2.337d**	30[b]
2.334	3-F	4-$B(OR)_2$ **2.338d**	32[b]
2.335	3-SO_2NEt_2	4-$B(OR)_2$ **2.338e**	40
2.336	3-$OCONEt_2$	4-$B(OR)_2$ **2.338f**	57[c]

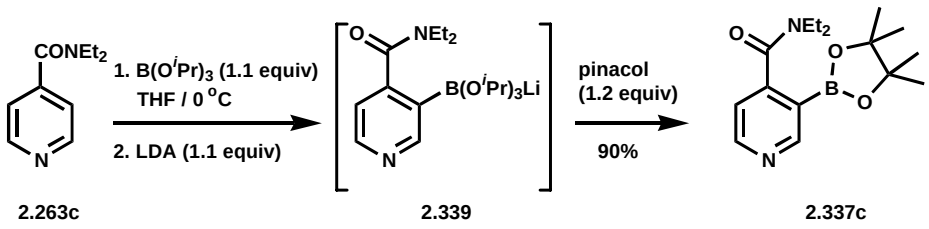
[a]Yields represent isolated materials after chromatography and recrystallization. [b]Complete metalation required 1.5 equiv.of LDA and $B(O^iPr)_3$. [c]Metalation was carried out at -78 °C.

As part of continuing efforts to develop D*o*M - cross coupling strategies,[183] our interest to provide dependable routes to pyridylboronic coupling partners led us to explore the possibility of a one-pot D*o*M-cross coupling protocol which would allow us to skip the tedious and often inefficient purification of the borylated products. Upon gaining direct access to a wide range of azabiaryls, we also aimed to demonstrate their synthetic potential beyond the inherent D*o*M chemistry. Thus, we set to briefly explore the application of the DreM reaction to substituted phenyl pyridinecarboxamides towards the synthesis of azafluorenones. These results are described below.

2.4. Results and Discussion

2.4.1. Pyridine Carboxamides. Optimization of the Metalation and Cross Coupling Steps

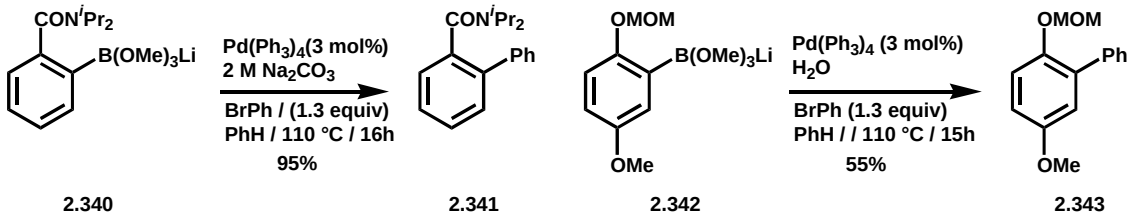
Preliminary experiments carried out by Green and Larkin established that Hawkins' conditions were suitable for the boronation of pyridine carboxamides. The optimization of these conditions (addition of LDA to a $B(O^iPr)_3$/substrate mixture in THF at 0 °C) was carried out on diethyl isonicotinamide (**2.263c**, Scheme 2.63) and, due to the difficult isolation of the free boronic acid corresponding to **2.339**, a measurement of the performance of this protocol had to rely on its conversion to the pinacol boronate **2.337c** which was analyzed by GC. Thus, the excess of LDA/$B(O^iPr)_3$ used by Green was reduced to 1.1-1.2 equivalents without observing any self condensation product while maintaining the high yields of the products obtained from this reaction.



Scheme 2.63

The optimization of the cross coupling step was also complicated by the water solubility and difficult separation of **2.337c**. In keeping with the *in situ* nature of the intended procedure and following a common practice with poorly isolable boronic acids, the crude material was used, after evaporation of the ethereal solvent, directly for the cross coupling reaction. Keay has described a similar protocol which, despite the

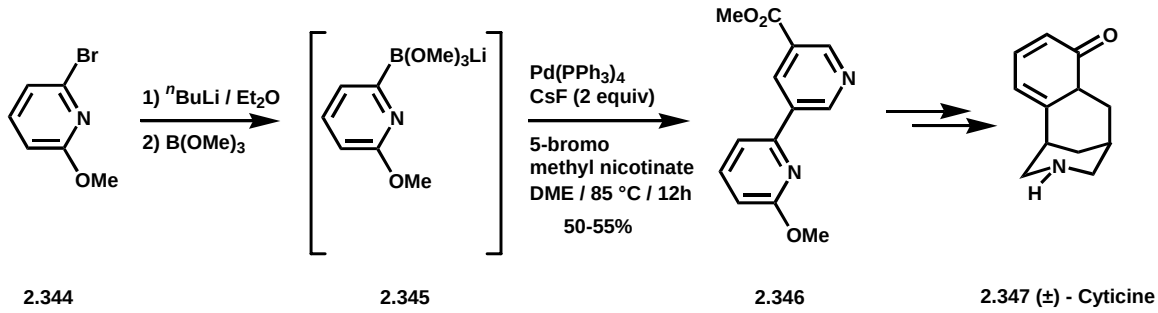
comparatively lower yields of coupling products, was superior to the two-step procedure (Examples given in Scheme 2.64).[184]



Scheme 2.64

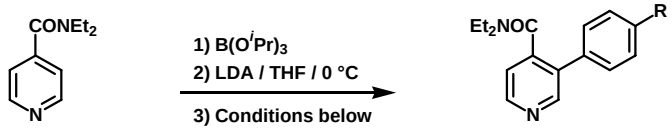
The crude mixtures from the reaction of metalation-boronation presumably contained the pyridylboron "ate" complex **2.339** which is the required intermediate for Suzuki coupling (Scheme 2.12); hence, hydrolysis of this intermediate appeared superfluous, and anhydrous conditions were used for the attempt to effect direct cross coupling. However, upon refluxing the crude pyridyl boron product metalation residue with excess of iodobenzene and $Pd(PPh_3)_4$ in dry and degassed toluene (a base was deemed unnecessary), tar formation was observed along with extensive deiodination (entry 1, Table 2.7). This result is, in fact, concordant with Keay's poor yield (9%) obtained when testing the otherwise successful (62%) coupling of bromobenzene and $PhB(O^iPr)_3Li$ in the absence of water and base.[184a] On the other hand, facing a similar isolation problem during his total synthesis of cyticine (**2.347)**, O'Neill resorted successfully to the coupling of the boronate complex **2.345** to give **2.346**, provided a source of fluoride was present (Scheme 2.65).[185] Despite the unclear role of CsF in this reaction, these conditions were tested on **2.263c** only to yield traces of the desired product **2.348a** (entry 2, Table 2.7). Concordantly with Green's early attempt, even Keay's optimized

conditions proved unproductive (entry 3) and it was therefore decided to pursue Green's preliminary cross coupling of the crude pyridyl boropinacolates.



Scheme 2.65

Table 2.7 Optimization of the One-Pot DoM-Boronation-Suzuki-Miyaura Cross Coupling of Diethyl Isonicotinamide



2.263c

2.348a R = H
2.348b R = CN

Entry	pinacol equiv	solvent	base (equiv)	PhI equiv	$Pd(PPh_3)_4$	yield
1	---	PhMe	---	10	5 %	tar formation[a]
2	---	PhMe	CsF (2)	10	5 %	traces[a]
3	---	PhMe	Na_2CO_3 aq. (5)	10	5 %	---[a]
4	2.0	PhMe	Na_2CO_3 aq. (5)	10	5 %	84 %
5	1.2	PhMe	Na_2CO_3 aq. (5)	2	5 %	94 %
6	1.2	PhMe	Na_2CO_3 aq. (5)	2	1 %	52 %
7	1.2	PhMe	Na_2CO_3 aq. (5)	1.1	5 %	84 %
8	1.2	PhMe	Na_2CO_3 aq. (5) + DIPA (1.1)	1.1 of *p*-BrC_6H_4CN	5 %	75 %
9	1.2	THF	Na_2CO_3 aq. (5)	as above	5 %	29 %
10	1.2	THF (MW)	Na_2CO_3 aq. (5)	as above	5 %	14 %

[a] Extensive dehalogenaion of the coupling partner was observed.

In the event, Green's protocol (cross coupling of the crude boropinacolate) succeeded to afford product **2.348a** in high yield (entry 4). The positive outcome of this reaction compared to the cross coupling the crude boron ate complex (entry 3) may possibly be

rationalized by consideration of the hindrance difference of the boron complexes (**2.339** and **2.349**, Fig 2.5).

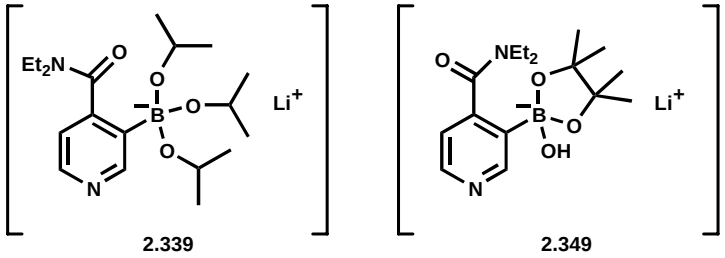
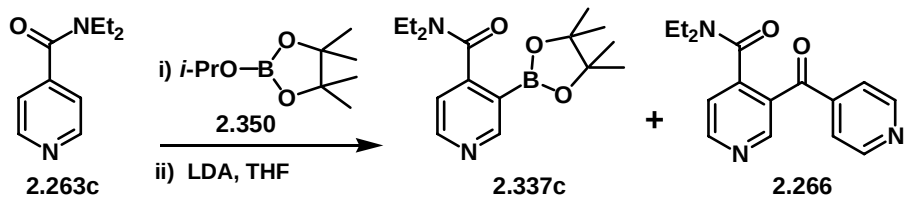


Figure 2.5 Two Competent Boron Ate Complexes in the Transmetalation Step of the Suzuki Reaction

Green's use of large excess of iodobenzene coupling partner was gradually reduced and 1.1 equivalent was eventually found a good compromise to give high yield of product (84%), as long as the catalyst load remained at 5% (entries 5-7). To test whether the solvent replacement of the metalation solvent could be avoided, the THF solution of the boropinacolate **2.337c** was added to the Suzuki reagent cocktail and the mixture was refluxed. DIPA contained in this solution, a byproduct of the metalation step normally removed with the solvent, was first tested for possible interferences with the coupling process. While a refluxing toluene solution of the crude pinacol ester spiked with DIPA returned a good yield (entry 8), the same mixture in THF gave a poor outcome (29%) due, most probably, to the lower temperature achievable (entry 9). Microwave irradiation of a THF solution of the coupling cocktail did not result in a better outcome and caused decomposition of the catalyst (entry 10). Since formation of the pinacol ester appeared a necessity, an attempt was made to quench the lithiated carboxamide **2.263c** with the borate **2.350** which, expectedly, was found compatible with LDA (Table 2.8). Tests at different temperatures showed that the boronation was favoured by higher temperatures. However, despite its somewhat more compact structure, **2.350**, even at rt, underwent

reaction more slowly than its open analogue $B(O^iPr)_3$ at 0 °C, leaving plenty of room for competitive undesired self condensation. Addition of the nicotinamide to a mixture of LDA / **2.350** did not substantially change the picture and, eventually, the first step of this protocol was carried out with 1.2 equiv of the inexpensive $B(O^iPr)_3$.

Table 2.8 DoM-Boronation of Diethyl Isonicotinamide with Borate 2.350 as Electrophile



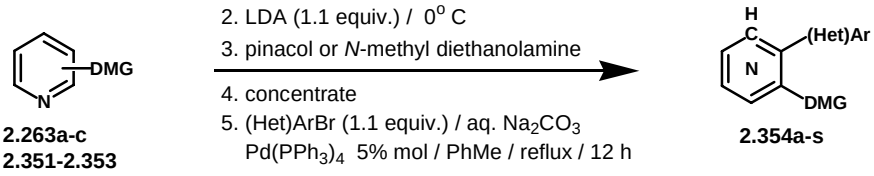
	-50 °C	15 %	80 %
	-30 °C	14 %	83 %
	-15 °C	18 %	77 %
	0 °C	21 %	72 %
	25 °C	54 %	41 %
2.350 + LDA (1) 1.397c, -78 C / 3 h; (2) aq. NH_4Cl, -30 C		48 %	47 %

2.4.2. Generalization of the One-Pot Synthesis of Azabiaryls 2.354a-s

Following the brief exploration of suitable conditions for the one-pot DoM-boronation-cross coupling of the isonicotinamide **2.263c** (Table 2.7), generalization of this protocol began with a thorough testing of the synthetically useful isomeric amide DMG-bearing pyridines **2.263a-c**. Thus, using selected aryl bromides, picolinamide **2.263a**, nicotinamide **2.263b**, isonicotinamide **2.263c** as well as 3-chloropyridine (**2.351)** and 2-fluoropyridine (**2.352)** were converted into a variety of functionalized azabiaryls **2.354a-d**, **2.354e-h**, **2.354i-m** (and **2.348b**), **2.354n-p** and **2.354q-r** respectively (Table 2.9)

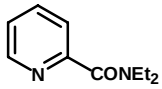
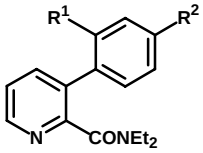
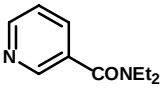
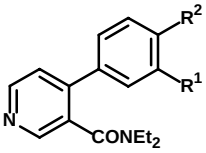
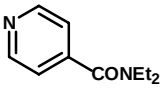
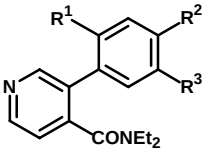
bearing electron-donating (MeO) and electron-withdrawing (Cl, CN, NO_2) substituents.[186]

Table 2.9 Synthesis of Azabiaryls through One-Pot D*o*M-Boronation-Suzuki-Miyaura Cross Coupling of Pyridine Derivatives



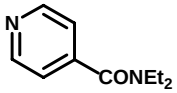
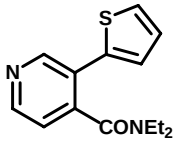
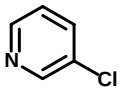
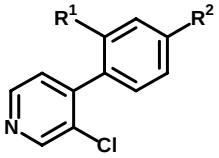
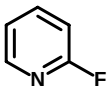
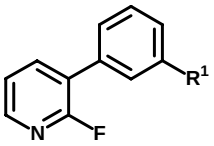
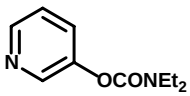
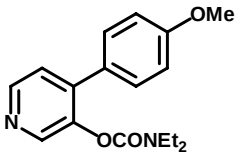
2.263a-c
2.351-2.353

2.354a-s

Entry	Pyridyl-DMG	Azabiaryl	yield (%)
			
	2.263a	**2.354**	
1		**a** : R^1 = H, R^2 = OMe	62
2		**b** : R^1 = H, R^2 = CN	71
3		**c** : R^1 = R^2 = OMe	37
4		**d** : R^1 = H, R^2 = NO_2	30[†]
			
	2.263b	**2.354**	
5		**e** : R^1 = H, R^2 = OMe	71[§]
6		**f** : R^1 = R^2 = OMe	42[§]
7		**g** : R^1 = H, R^2 = CN	73[§]
8		**h** : R^1 = OMe, R^2 = H	57
			
	2.263c	**2.354**	
9		**i** : R^1 = R^2 = OMe; R^3 = H	33
10		**j** : R^1 = R^3 = H; R^2 = OMe	75
11		**2.348b** : R^1 = R^3 = H; R^2 = CN	76
12		**k** : R^1 = R^2 = H; R^3 = Cl	61
13		**l** : R^1 = $CONEt_2$, R^2 = R^3 = H	67

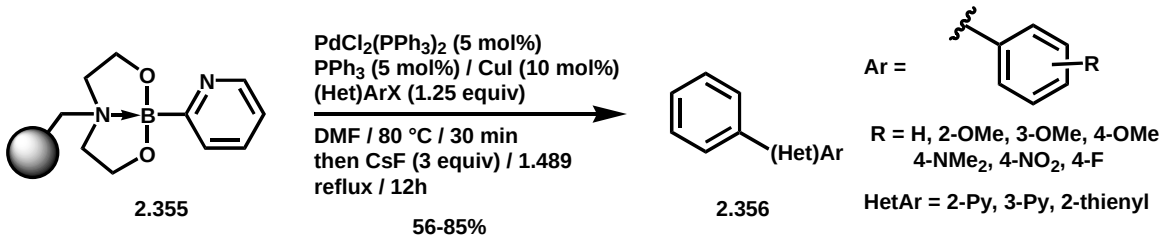
[†]Prepared by Sunny Lai; [§]Prepared by Kevin A. Ogilvie.

Table 2.9 Synthesis of Azabiaryls through One-Pot D*o*M-Boronation-Suzuki-Miyaura Cross Coupling of Pyridine Derivatives (Cont'd)

Entry	Pyridyl-DMG	Azabiaryl	Yield (%)
14			85
	2.263c	**2.354m**	
			
	2.351	**2.354**	
15		**n** : R^1 = H, R^2 = OMe	48[a§]
16		**o** : R^1 = H, R^2 = CN	55[a§]
17		**p** : R^1 = H, R^2 = NO_2	43[a§]
			
	2.352	**2.354**	
18		**q** : R^1 = OMe	68[§]
19		**r** : R^1 = Cl	73[§]
18			64[b]
	2.353	**2.354s**	

[a] Metalation was carried out at -78 °C. [b] Reagents and conditions: (i) $B(O^iPr)_3$ (1.1 equiv)/THF. (ii) LDA (1.1 equiv)/-78 °C to rt. (iii) $MeN(CH_2CH_2OH)_2$, 0 °C, 2h. (iv) Concentrate. (v) *p*-Bromoanisole (0.67 equiv), K_2CO_3 (3 equiv), $Pd(OAc)_2$ (5%), S-Phos (10%), CuI (10%), degassed EtOH, reflux 3h. [§]Prepared by Kevin A. Ogilvie.

Reasonable yields of products were obtained, with the exception of those involving coupling with electron rich aryl bromides (entries 3, 6, 9). This trend is expected because EDG-bearing aryl bromides decelerate the oxidative addition to Pd(0) which is generally the rate determining step.[187] The comparably lower yields of chloro azabiaryls (entries 15-17), may be rationalized by consideration of the known instability of the lithiated species to pyridine formation,[82,188] while the unexpected poor performance of this protocol on *p*-bromonitrobenzene (entry 4) remains unexplained.[189] In most cases, the product mixtures were contaminated with unidentified impurities that imposed requirement for high vacuum distillation at high temperature to obtain analytically pure samples which led to unavoidable erosion of the isolated yields. Hodgson and Salingue have recently succeeded in the first cross coupling of the *N*-phenyl diethanolamine ester of 2-pyridyl boronic acid with several aryl iodides under $Pd(OAc)_2$/CuI co-catalysis. This protocol appeared to be synthetically useful only for activated (EWG-bearing) aryl iodides; however Gros and Fort's adaptation of these conditions for solid support succeeded in the coupling of a 2-pyridylboronic ester with (het)aryl bromides in good yield (Scheme 2.66).[190]

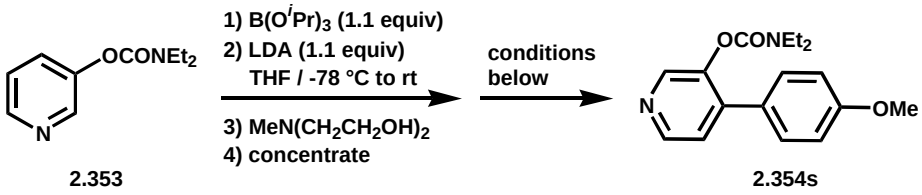


Scheme 2.66

Unlike for the cross coupling of boronic acids and their pinacolates, no standard conditions exist for the coupling of their diethanolamine counterparts and, except for the

above recent contributions, their acidic hydrolysis to the corresponding free boronic acids represented an obligatory step to their use in Suzuki coupling reactions. Thus, having chosen *p*-bromoanisole as coupling partner for the D*o*M-Suzuki sequence of carbamate **2.353** (Table 2.10), a wide screening of reaction conditions was carried out, always in the presence of CuI. Gratifingly, these tests led to the selection of the pair $Pd(OAc)_2$/S-Phos as catalyst/ligand combination, which, under conditions of brief reflux in ethanol, effected the cross coupling of the *N*-methyl diethanolamine 3-boronic ester derivative of **2.353** and yielded 64% of the desired azabiaryl **2.354s** (entry 2). The application of Gros and Fort's original conditions led, instead, to only 24% yield of azabiaryl **2.354s** (entry 1). More focused experiments underlined the critical role of CuI for the formation of the desired azabiaryl (entry 4), defined the minimum catalyst/ligand load (5%, entry 3) and excluded the possibility of coupling aryl chlorides under these conditions (entry 5).

Table 2.10 Cross Coupling Test for *N*-Methyl Diethanolamine Boronate of 2.353



2.353 2.354s

entry	halide	catalyst / ligand	solvent	CuI (%)	Yield (%)
1	$MeOC_6H_4Br$ (1.25 equiv)	$PdCl_2(PPh_3)_2$ (5 mol%) PPh_3 (10 mol%) CsF (3 equiv)	DMF reflux / 10h	10	24
2	$MeOC_6H_4Br$ (0.67 equiv)	$Pd(OAc)_2$ (5 mol%) S-Phos (10 mol%) K_2CO_3 (3 equiv)	EtOH reflux / 10h	10	64
3	$MeOC_6H_4Br$ (0.67 equiv)	$Pd(OAc)_2$ (3 mol%) S-Phos (6 mol%) K_2CO_3 (3 equiv)	EtOH reflux / 10h	10	31
4	as in entry 3	as in entry 3	as in entry 3	----	----
5	$MeOC_6H_4Cl$ (0.67 equiv)	as in entry 2	as in entry 2	10	----

2.4.3. Synthesis of Azafluorenones

Azabiaryl 2-carboxylic acids and esters are precursors of choice for the synthesis of azafluorenones, namely through intramolecular Friedel-Crafts reactions as has been demonstrated under zeolite catalysis,[191] or, more often, under harsh conditions based on PPA, H_2SO_4 or $AlCl_3$ as catalysts.[192] The interest in these systems is mainly due to the occurrence of the 4-azafluorenone skeleton in the antifungal alkaloid onychine (**2.357**, Fig. 2.6) isolated from *Onychopetalum amazonicum* and *Cleistopholis patens*, as well as in at least 14 onychine derivatives bearing hydroxyl and methoxy groups in the benzene ring.[193] In 1991, Snieckus opened a new route to azafluorenones **2.358** and **2.359** using a directed remote metalation (DreM) strategy.[194] More recently, similar remote metalations have also been carried out on pyridoylbenzoic acids and esters as well as on pyridyloxybenzamides to obtain azaanthraquinones **2.363** and **2.364**[195] and azaxanthones **2.361** and **2.362**,[196] respectively. Using the DreM approach, Quéguiner has prepared three analogous products (**2.359**, **2.360**, Fig. 2.6 and **2.366**, Scheme 2.67) from all isomeric *ortho*-pyridylbenzoic acids or their ethyl esters.[197]

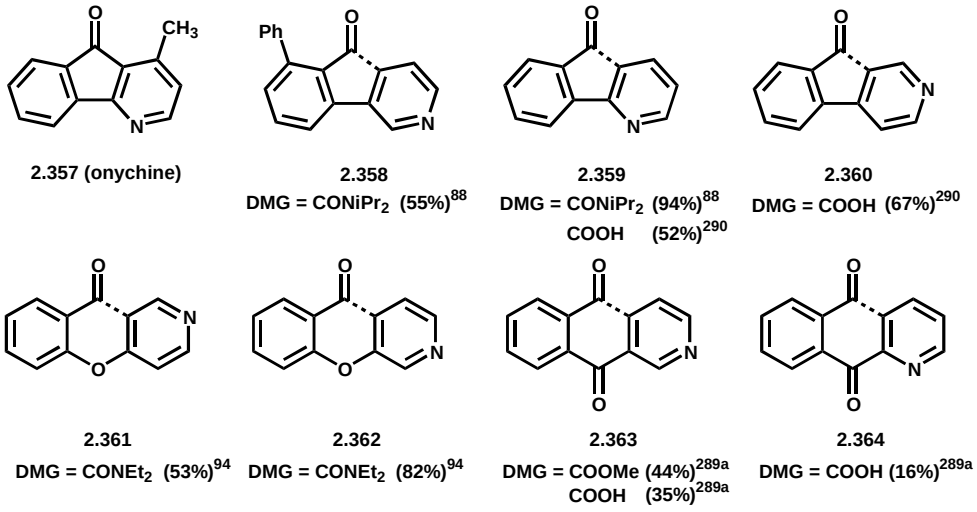
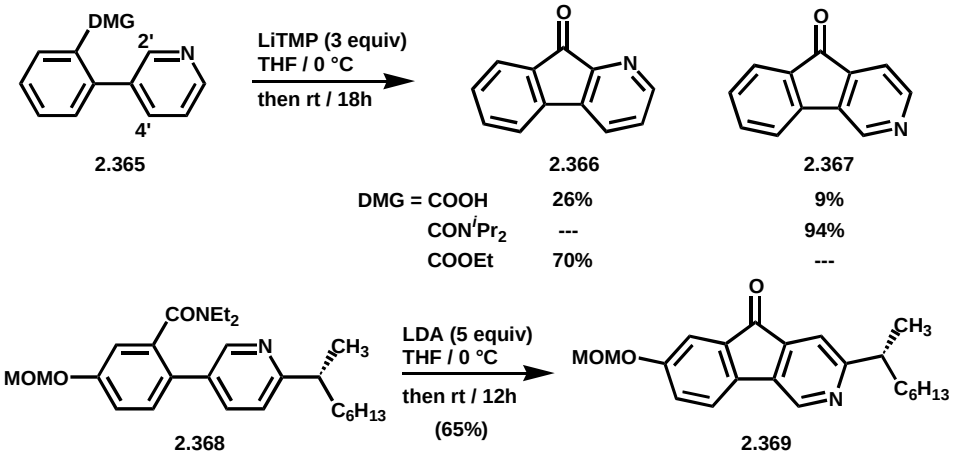


Figure 2.6 Examples of Aza -fluorenones, -anthraquinones and –xanthones Obtained through DreM Reaction

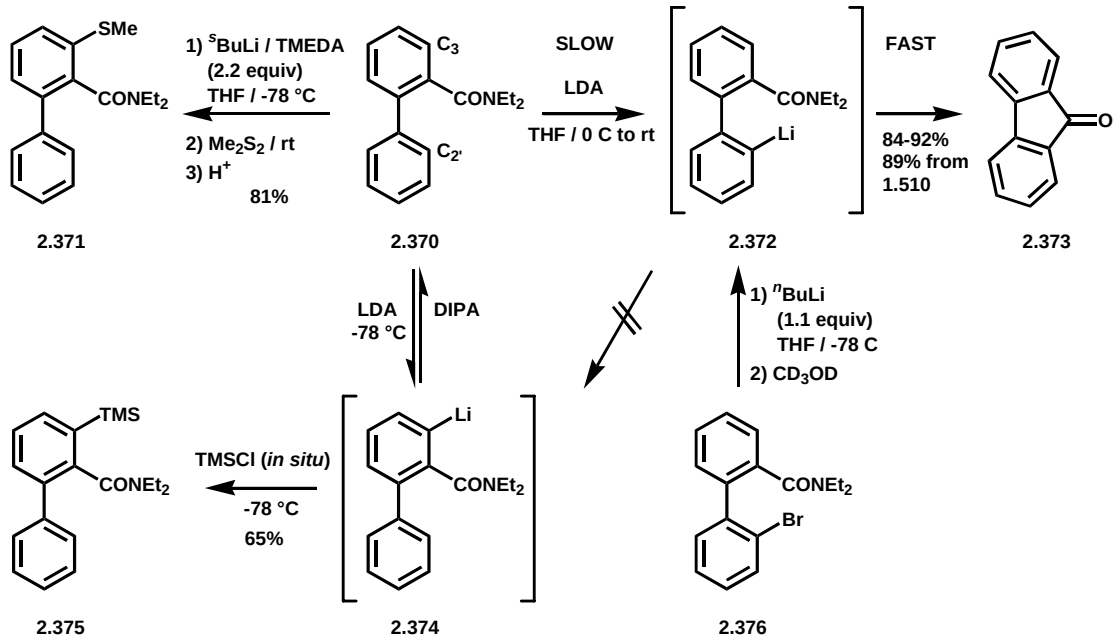
The pyrid-3-yl benzoic acid **2.365**, which in theory may be deprotonated at both $C_{2'}$ and $C_{4'}$ remote positions, undergoes a non regioselective cyclization to give two isomeric azafluorenones **2.366** and **2.367** (Scheme 2.67). Mortier has recently studied the mechanism of this reaction and has found that the isomeric ratio depends on the electrophilicity of the DMG.[198]



Scheme 2.67

When the remote metalation is directed by the highly electrophilic COOEt group, the kinetic anion at $C_{2'}$ rapidly undergoes cyclization to give only **2.366**. However, when the DMG is the less electrophilic CON^iPr_2, the $C_{2'}$ anion, whose trapping with a D^+ source was not attempted, may undergo equilibration to the thermodynamically more stable $C_{4'}$ isomer which leads to the azafluorenone **2.367**. The same regioselectivity was observed by McCubbin, Lemieux, and Snieckus in the conversion of **2.368** to the azafluorenone (**2.369**) constituting a liquid crystalline material (Scheme 2.67).[199] A thorough study on the DreM of biaryl **2.370** has been carried out (Scheme 2.68).[200] C_3-Deprotonation was demonstrated to occur at −78 °C both with ^{s}BuLi/TMEDA and with LDA. However, when generated under kinetic conditions (**2.370** → **2.371**), the *o*-

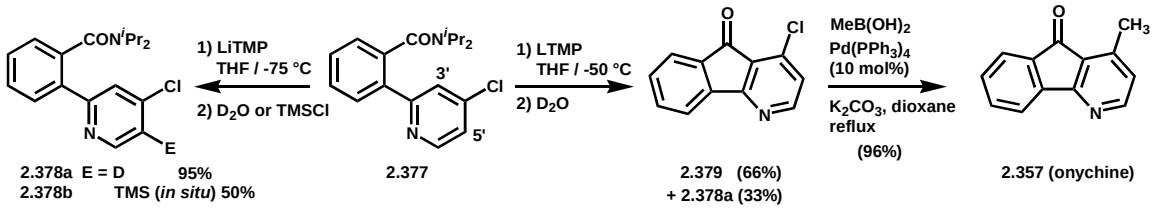
lithiated intermediate **2.374** was stable at rt and was trapped with Me_2S_2 in 81% whereas, under thermodynamic conditions (LDA), it could be trapped in 65% at −78 °C only in the presence of *in situ* TMSCl.



Scheme 2.68

In the absence of an *in situ* electrophile, the lithiation of **2.370** with LDA gave exclusively **2.373** with erosion of the deuterium content (**2.375**-1d_0:**2.373**-1d_1 22:78) if the reaction was performed on **2.370**-3d_1 (3d_0:3d_1 1:99). Lithium-halogen exchange of bromide **2.376** followed by CD_3OD addition furnished **2.373**-1d_0 (89%) suggesting that the cyclization step is much faster than the equilibration of **2.372** to **2.375**. On the basis of these combined observations, a mechanistic rationale was proposed for the formation of **2.373** that, following a CIPE of the **2.370**/LDA complex, invokes the equilibrium and non-productive formation of **2.374**. At the same time, the complex also promotes the rate–determining and irreversible $C_{2'}$ deprotonation of **2.370** which results in the rapid cyclization to fluorenone (**2.375**), the latter being the driving force for the process.

Interestingly, the deprotonation of chloro-substituted azabiaryl **2.377** with LiTMP at -75 °C followed by external (D_2O) and *in situ* quench (TMSCl) leads to the azabiaryls **2.378a** and **2.378b** (Scheme 2.69).[201] However, if **2.377** is lithiated at –50 °C, the azafluorenone **2.379** is obtained as the main product, the remaining material being **2.378a**. This suggest that, as temperature increases, the kinetic $C_{5'}$-anion formed at low temperature equilibrates with the thermodynamic $C_{3'}$-anion generated following a CIPE and the latter is rapidly trapped by the amide group in the cyclization step to the azafluorenone **2.379**. The product **2.379**, following cross coupling with methylboronic acid, yielded onychine (**2.357)** in excellent yield.

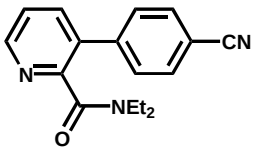
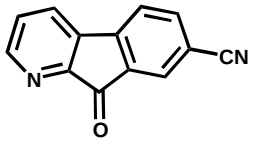
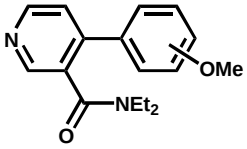
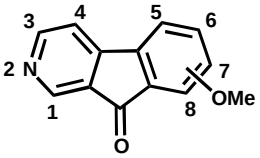
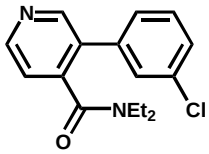
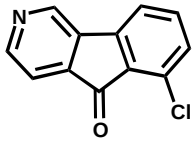


Scheme 2.69

The DreM reaction of **2.354a-m** would differ from all known examples of anionic cyclization of azabiaryls (Fig. 2.6, Schemes 2.67 and 2.69) because the remote deprotonation must occur on the phenyl ring instead of the more acidic pyridine ring. However, since the reaction is strongly driven by the irreversible intramolecular cyclization, small equilibrium concentrations of the remotely lithiated species were expected to lead to the fluorenone products. Thus, using variable amounts of LDA, selected azabiaryls **2.354b,e,h,k** were cyclized to the expected azafluorenones (Table 1.11). The metalation of EWG-bearing azabiaryls **2.354b** and **2.354k** required less LDA and occurred at lower temperature than did the electron-rich **2.354e** and **2.354h** whereas

in the DreM of **2.354b**, 1 equivalent of LDA was presumably used up by reversible nucleophilic addition to the CN group.[202]

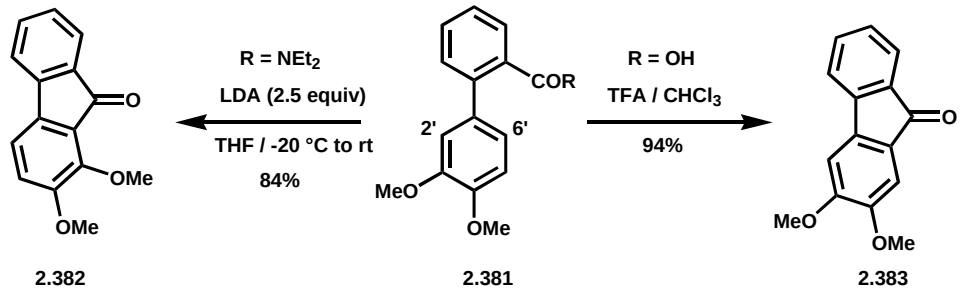
Table 2.11 Synthesis of Substituted Azafluorenones 2.380a-d *via* DreM of Azabiaryls

Azabiaryl	Conditions	Azafluorenone	Yld, %
	A		55
2.354b		**2.380a**	
			
2.354e (R = 4'-OMe)	B	**2.380b (R = 7-OMe)**	56
2.354h (R = 3'-OMe)	B	**2.380c (R = 8-OMe)**	63
	C		81
2.354k		**2.380d**	

A: LDA (2 equiv.) / THF / -78 to -10 °C / 90 min; B: LDA (3 equiv.) / THF / -40 to 10 °C / 120 min; C: LDA (1.5 equiv.) / THF / -50 °C / 90 min.

Interestingly, regioselective cyclization of **2.354h** and **2.354k** to **2.380c** and **2.380d**, respectively, is observed, an indication of the directing effect of the strong OMe and weak Cl DMG.[203] Thus the products of cyclization are complementary to the Lewis acid-mediated processes. As a matter of fact, when heated in PPA, the carboxylic acid corresponding to **2.354h** is reported to afford an approximatively 1:1 mixture of **2.380c** and the isomeric 6-methoxy-2-azafluorenone (72% combined yield) and requires chromatographic separation.[204] Under Friedel-Crafts conditions, even the carboxylic acid corresponding to symmetrically substituted **2.354e** is described to be poorly converted

into **2.380b** (35%), as expected from the deactivation due to the OMe group.[205] Since **2.380a** and **2.380d** have not been prepared by Friedel-Crafts reaction of the carboxylic acid corresponding to **2.354b** and **2.354k**, respectively, a direct comparison cannot be made. However, in the first case, sensitivity of the cyano group to PPA or Lewis acid-catalyzed hydrolysis would be expected. Such complementarity between the Friedel-Crafts and DreM reactions has been usefully exploited in the synthesis of isomeric dimethoxyfluorenones **2.382** and **2.383** (Scheme 2.70) as potential kinase inhibitors.[Error! Bookmark not defined.] Thus, under acidic conditions, electrophilic substitution of **2.381** is, expectedly, $C_{6'}$-, *i.e.*, *para*-selective to give **2.383** while, under anionic conditions, the OMe DMG effect is operative at $C_{2'}$ together with a CIPE to afford the isomeric **2.382** (Scheme 2.70).

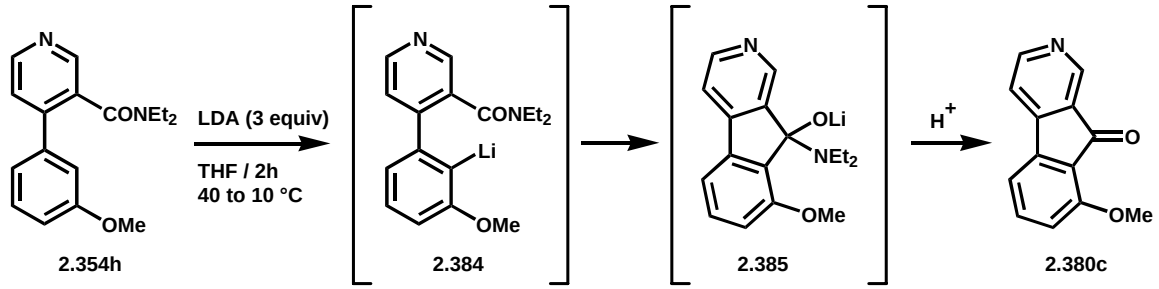


2.382 **2.381** **2.383**

Scheme 2.70

The DreM reaction was conveniently monitored by React-IR in one selected case (**2.354h→2.380c**). The disappearance of the amide carbonyl stretching frequency (ν = 1632 cm^{-1}, Fig. 2.7) of the starting amide **2.354h** as a function of time is observed upon gradual addition of 3 equiv of LDA. It is only after addition of MeOH that the stretching absoption of the carbonyl (ν = 1718 cm^{-1}) representing **2.380c** increases in intensity. These results strongly suggest the expected formation of a tetrahedral carbinolamine

alkoxide **2.385** which has been the long-assumed reasonable intermediate for the DreM reaction (Scheme 2.71).[200a] This observation also indicates that the tetrahedral intermediate is quite stable under anionic conditions unlike that derived from the urea **1.92** (Scheme 1.19) which, through the same analytical technique, was shown to decompose instantly before quenching with an aqueous NH_4Cl solution.[206]



Scheme 2.71

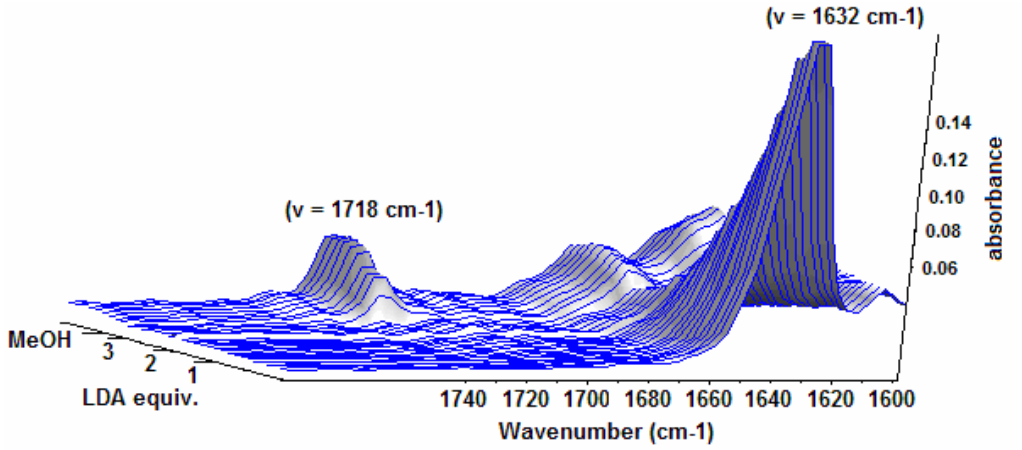


Figure 2.7 DreM of 2.354h through the Lens of React-IR

2.5 Conclusions

The compatible base-electrophile combination, as originally established by Martin with LiTMP/TMSCl for *in situ* trapping of equilibrium concentrations of aryl carbanions, and subsequently developed by Hawkins for LDA-$B(OR)_3$ (Scheme 2.61) was applied, following initial work in the Snieckus laboratories[178,180] to a D*o*M-boronation sequence

for a series of DMG-bearing pyridines. Thus, a general DoM methodology was established for the preparation of all isomeric *N*,*N*-diethyl pyridinecarboxamide boronic acid derivatives isolated as their pinacolates and/or diethanolamine adducts (**2.337** and **2.338**, respectively, Table 2.6). For this series, results show that, using $B(O^iPr)_3$, the otherwise unavoidable self-condensation of the lithiated intermediates (Scheme 2.53)[141a] is completely prevented. With these results in hand, the optimization of the Suzuki cross coupling reaction of the crude pyridyl boronate **2.337c** (Table 2.7) was accomplished, establishing that the notoriously difficult isolation and purification of pyridyl boronates is not required. The one-pot D*o*M-boronation and Suzuki-Miyaura protocol was thus applied to all three isomeric pyridine carboxamides **2.263a-c** and extended to chloro- and fluoropyridines pyridines **2.351** and **2.352** respectively, which do not have the option to undergo self-condensation before external quench (Table 2.9). With standard catalyst loading, this one-pot metalation-cross coupling procedure gave a wide series of azabiaryls in acceptable yields using deactivated aryl bromide coupling partners. Selected DMG-bearing azabiaryls **2.354b,e,h,k** were in turn subjected to directed remote metalation (DreM) reaction to furnish substituted azafluorenones **2.380a-d** (Table 2.11). For 3′-substituted azabiaryls **2.354h,k**, exclusive formation of one azafluorenone isomer (**2.380c,d**) was observed, proving that, as in 1,3-disubstituted aromatic systems, a strong synergy can exist between two DMGs despite their placement in alternate rings. Hence, another piece has been added to the mosaic of the DreM reaction. Finally, the DreM reaction of **2.354h** (Scheme 2.71) was monitored by React-IR and suggestive evidence was obtained for the presence of tetrahedral carbinolamine alkoxide intermediate **2.375**.

2.6. Experimental Section

General Methods

Melting points are uncorrected and represent values obtained on recrystallized materials with a Fisher Scientific melting point apparatus. IR spectra were recorded as films or as KBr pellets using a BONEM FT-IR spectrophotomer. NMR spectra were recorded on a Brucker Avance-300, 400 or 500 MHz. Low-resolution mass spectra (LRMS) were performed on an Agilent Technologies GC-MS system (6890N network GC system and 5973 Mass selective detector). High resolution mass spectra (HRMS) were recorded on a Kratos Mass Spectrometer or on a Micromass 70-250S Double Focusing Mass Spectrometer. The React-IR study was carried out with a Mettler Toledo ReactIR™ 4000 equipped with a SiComp sensor. The collection of the crystallographic data was performed on a Bruker SMART CCD 1000 X-ray diffractometer with graphite-monochromated Mo K_α radiation (λ = 0.71073 Å), operating at 50 kV and 30 mA over 2θ ranges of 3.86 ~ 56.62º at –93 °C controlled with Crysostream Controller 700. Diethyl ether and THF were freshly distilled from sodium under argon using benzophenone as indicator or were obtained anhydrous by forced passage through activated alumina in a Pure-Solv 400 solvent purification system (Innovative Technology, Inc.), whereas anhydrous hexanes and DMF were purchased from Sigma-Aldrich Chemical Co. Anhydrous dioxane, toluene, DME (Aldrich) and 2M aq. Na_2CO_3 were degassed through prolonged (1h) argon bubbling while sonicating the liquid in a Fisher L R Ultrasonic Bath. Alkyllithiums were purchased from Sigma-Aldrich and were titrated biweekly against *sec*-butanol using 1,10-phenanthroline as indicator or through reaction with *N*-benzylbenzamide to a blue endpoint. Anhydrous diisopropylamine,

diethylamine and 2,2,6,6-tetramethylpiperidine (HTMP) obtained from Sigma-Aldrich were stored over KOH and under argon. POPd2 was a gift of Combiphos Catalysts, Inc. whereas $Pd[PPh_3]_4$, $Pd_2(dba)_3$ and S-Phos were purchased from Strem Chemicals, Inc. $BrCF_2CF_2Br$ was purchased from Synquest Fluorochemicals and Cl_2CHOMe was purchased from Fluka. Diethyl nicotinamide was obtained from Aldrich and redistilled under high vacuum. All other commercial chemicals were purchased form Sigma-Aldrich. All experiments were carried out under argon in flame-dried glassware, using syringe-septum techniques. Unless otherwise indicated, reaction temperature values refer to the actual reaction mixtures as measured through a thermocouple thermometer (Barnant 600-1040) equipped with a type J temperature probe. Flash column chromatography was carried out using Silicycle Silia-P Flash Silica Gel (particle size: 40-63 μm, 60A). The frase "NH_4Cl quench" is intented to mean the addition of a saturated aqueous solution of NH_4Cl. Standard work-up refers to the extraction of a crude product from a mixture of EtOAc and a saturated solution of NH_4Cl or other given aqueous solution. Extraction cycles were repeated (generally 3 times) with fresh EtOAc until the organic layer displayed no absorption of UV light (λ = 254 nm). The combined organic layers were dried over anhydrous Na_2SO_4, subjected to filtration and then concentrated *in vacuo*. A solution of $ZnCl_2$ (1M) in THF was prepared as follows: a tared 250 mL two-neck flask was charged with ~ 0.1 mol of reagent grade $ZnCl_2$ (Fisher) and a glass stopper was fitted to one neck. The other neck was fitted with a glass stopcock connected to a high vacuum pump. While under vacuum, the salt was melted over a butane flame and then allowed to cool down. The flask was filled with Ar, weighed and the amount of anhydrous $ZnCl_2$ was calculated. The glass stopper was rapidly replaced with a rubber

septum under a stream of argon and a measured volume of anhydrous THF was introduced to obtain a 1M solution. The mixture was vigorously shaken and aged until it became clear (~ 1 week).

General Procedures

A. Preparation of a 0.7 M LDA solution. A stock solution of LDA (10 mL, 0.7 M) was prepared by dropwise addition of a solution of ^{n}BuLi (7 mmol) in hexanes to diisopropylamine (8.4 mmol, 1.2 mL) in the required volume of THF at –10 °C. The clear solution was stirred at 0 °C for 10 min before use.

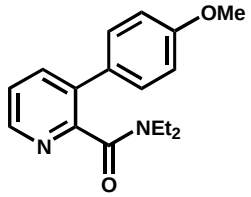
B. One-Pot D*o*M – Boronation – Suzuki-Miyaura Cross Coupling of Pyridine Derivatives 2.263a-c. A 50 mL flame-dried round bottom flask was charged with the pyridine carboxamide (2.8 mmol), THF (5 mL) and $B(O^{i}Pr)_3$ (3.08 mmol). To this solution cooled to -10 °C, LDA (4.40 mL, 3.08 mmol, 0.7M) stock solution, prepared as in procedure A, was added and the mixture was stirred at 0 °C for 45 min, monitoring the progress of the reaction by TLC (CH_2Cl_2/MeOH 9.5/0.5). Upon complete disappearance of the starting material, pinacol (0.40 g, 3.36 mmol) was added and the mixture was allowed to warm to rt with stirring over 1 h. The solvent was evaporated to dryness *in vacuo* and $Pd(PPh_3)_4$ (0.162 g, 0.14 mmol, 5 % mol) and the bromide (3.08 mmol) were added with care to minimize exposure of the mixture to air. After flushing briefly with argon, a water condenser was fitted to the flask and a degassed 2 M aqueous solution of Na_2CO_3 (7 mL, 14 mmol) and degassed toluene (5 mL) were added through a septum sealing the top of the condenser. The mixture was refluxed for 12 h, cooled, and extracted with EtOAc (6 x 10 mL). The combined organic extract was washed with brine

(40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude oily product was purified by the appropriate method to give the desired azabiaryl.

C. Directed remote Metalation of Azabiaryls 2.354b,e,h,k. A 50 mL flame-dried round bottom flask was charged with the azabiaryl in THF and LDA (prepared as in General Procedure A) was added to this solution while maintaining the given internal temperature. Upon complete disapperance of the starting material, the reaction mixture was quenched with NH_4Cl and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic extract was washed with brine, dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo*. The residue was subjected to the appropriate purification method.

Syntheses of azabiaryls 2.354a-d, 2.354h-m, 2.348b and 2.354s[207]

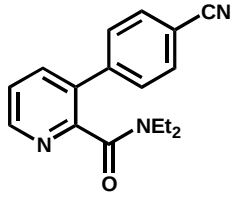
***N*,*N*-Diethyl-3-(4-methoxyphenyl)picolinamide (2.354a)**



Prepared according to General Procedure B from **2.263a** (0.5 g, 2.8 mmol) and 4-bromoanisole (0.56g, 3.08 mmol). Flash chromatography (CH_2Cl_2/MeOH 19.65/0.35) of the crude residue and Kugelrohr distillation (150 °C/0.13 mmHg) afforded **2.354a** (62% yield) as clear oil, IR (film) ν_{max} 1637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 7.72 (d, 1H, J = 8 Hz), 7.44 (d, 1H, J = 8 Hz), 7.36 (dd, 2H, J = 8.0, 4.8 Hz), 6.94 (d, 2H, J = 8 Hz), 3.83 (s, 3H), 3.43 (q, 2H, J = 7.2 Hz), 2.88 (q, 2H, J = 7.2 Hz), 1.04 (t, 3H, J = 7.2 Hz), 0.84 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 159.7, 153.4, 147.6, 137.1, 133.9, 130.0, 129.4, 123.5, 114.0, 55.2, 42.4, 38.6, 13.4, 12.2; EI

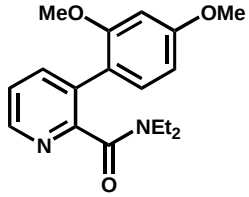
LRMS *m/z* (rel. intensity %) 284 (M^+, 61), 269 (5), 255, (3), 213 (40), 212 (22), 185 (64), 184 (44); 72 (100); HRMS calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1534.

3-(4-Cyanophenyl)-*N*,*N*-diethylpicolinamide (2.354b)



Prepared according to General Procedure B from **2.263a** (0.5 g, 2.8 mmol) and 4-bromo-benzonitrile (0.56 g, 3.08 mmol). Flash chromatography (CH_2Cl_2/MeOH 19.75/0.25) and recrystallization afforded **2.354b** (71% yield) as colourless needles, mp 140.5-142 °C (hexanes/EtOAc); IR (KB) ν_{max} 2223, 1632 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.63 (dd, 1H, *J* = 4.8, 1.6 Hz), 7.77 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.72 (d, 2H, *J* = 8 Hz), 7.60 (d, 2H, *J* = 8.8 Hz), 7.43 (dd, 1H, *J* = 8.0, 4.8 Hz), 3.38 (q, 2H, *J* = 7.2 Hz), 2.93 (q, 2H *J* = 7.2 Hz), 0.99 (t, 3H, *J* = 7.22 Hz), 0.91 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.0. 154.3 149.5, 142.6, 137.8, 133.2, 132.8, 130.1, 124.3, 119.0, 112.6, 43.1, 39.3, 12.9, 12.5; LRMS *m/z* (rel. intensity %) 280 (M+1, 6), 279 (34), 264, (6), 207 (22), 179 (94), 100 (7), 72 (100); HRMS calcd for $C_{17}H_{17}N_3O$ 279.1372, found 279.1377.

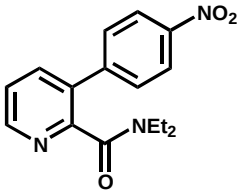
***N*,*N*-Diethyl-3-(2,4-dimethoxyphenyl)picolinamide (2.354c)**



Prepared according to General Procedure B from **2.263a** (0.5 g, 2.8 mmol) and 1-bromo-2,4-dimethoxybenzene (0.67 g, 3.08 mmol). Flash chromatography (CH_2Cl_2/MeOH 19.6/0.4) of the crude residue and distillation (170 °C / 0.6 mmHg) afforded **2.354c** (37% yield) as a thick clear oil, IR (film) ν_{max} 1636 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 8.53 (dd, 1H, *J* = 4.8, 1.5 Hz), 7.73 (d, 1H, *J* = 7.8, 1.5 Hz), 7.35 (dd, 1H, *J* = 7.8, 4.8 Hz), 7.21 (d, 1H, *J* = 9.0 Hz), 6.55 (m, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 3.36 (q, 2H, *J* = 7.2

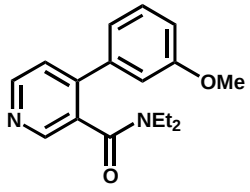
Hz), 3.04 (q, 2H, J = 7.2 Hz), 1.03 (t, 3H, J = 7.2 Hz); 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.4, 161.9, 158.2, 152.7, 148.5, 145.0, 132.7, 132.4, 121.2, 118.2, 105.0, 99.0, 55.94, 55.90, 42.7, 38.7, 14.0, 12.5; LRMS *m/z* (rel. intensity %) 314 (M^+, 46), 283 (12), 243, (47), 214 (100), 199 (57), 184 (44), 156 (24); HRMS calcd for $C_{18}H_{22}N_2O_3$ 314.1630, found 314.1632.

_N_,_N_-Diethyl-3-(4-nitrophenyl)picolinamide (2.354d)



Prepared according to General Procedure B from **2.263a** (0.5 g, 2.8 mmol) and 1-bromo-4-nitrobenzene (0.622 g, 3.08 mmol). Flash chromatography (Hexanes/EtOAc 4/1) of the crude residue and recrystallization furnished **2.354d** (37% yield) as pale yellow plates, mp 127-128 °C (Hexanes/CH_2Cl_2); IR (KBr) ν_{max} 1628, 1512, 1351 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (dd, 1H, J = 4.7, 1.5 Hz), 8.28 (d, 2H, J = 8.8 Hz), 7.79 (d, 1H, J = 7.9, 1.5 Hz), 7.69 (d, 2H, J = 8.8 Hz), 7.46 (1H, dd, J = 7.9, 4.7 Hz), 3.44 (q, 2H, J = 7.0 Hz), 2.99 (q, 2H, J = 7.0 Hz), 1.05 (t, 3H, J = 7.3 Hz), 0.96 (t, 3H, J = 7.04 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 153.6, 149.2, 147.7, 143.9, 137.4, 132.4, 129.8, 123.9, 123.7, 42.7, 39.0, 13.6, 12.3; LRMS *m/z* (rel. intensity %) 299 (M^+, 16), 269 (14), 228 (8), 227 (11), 200 (20), 199 (35), 72 (100); HRMS calcd for $C_{16}H_{17}N_3O_3$ 299.1270, found 299.1275.

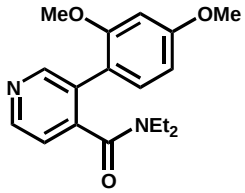
_N_,_N_-Diethyl-4-(3-methoxyphenyl)nicotinamide (2.354h)



Prepared according to General Procedure B from **2.263b** (1.5 g, 8.4 mmol) and 3-bromoanisole (1.73 g, 9.24 mmol). Flash chromatography (EtOAc/MeOH 9.65/0.35) afforded **2.354h** (57%

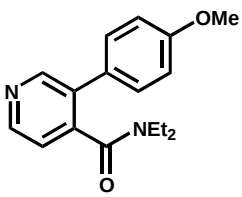
yield) as a clear oil, IR (film) ν_{max} 1631, 1579, 1433, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, 1H, J = 5.1 Hz), 8.60 (s, 1H), 7.38-7.31 (m, 2H), 7.11-7.06 (m, 2H), 6.99-6.94 (m, 1H), 3.83 (s, 3H), 3.65-3.90 (bs, 1H), 3.20-3.65 (m, 3H), 0.99 (t, 3H, J = 4.2 Hz), 0.78 (t, 3H, J = 4.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 159.7, 150.0, 147.9, 145.8, 138.5, 131.9, 129.8, 123.4, 120.8, 114.8, 113.8, 55.4, 42.5, 38.7, 13.5, 12.0; LRMS *m/z* (rel. intensity %) 284 (M, 26), 283 (74), 213 (17), 212 (100), 185 (12), 169 (27); HRMS calcd for $C_{17}H_{19}N_2O_2$ (M-H) 283.1447, found 283.1436.

***N*,*N*-Diethyl-3-(2,4-dimethoxyphenyl)isonicotinamide (2.354i)**



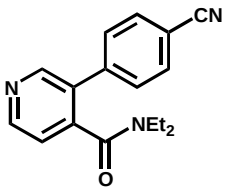
Prepared according to General Procedure B from **2.263c** (0.5 g 2.8 mmol) and 1-bromo-2,4-dimethoxybenzene (0.67 g, 3.08 mmol). Flash chromatography (CH_2Cl_2/MeOH 19.75/0.25) of the crude material followed by Kugelrohr distillation (156 °C/0.13 mmHg) afforded **2.354i** (33% yield) as colourless oil, IR (film) ν_{max} 3483, 1628 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.56 (s, 1H), 8.52 (d, 1H, J = 4.8 Hz), 7.22 (dd, 1H, J = 4.8, 0.8 Hz), 7.16 (dd, 1H, J = 7.6, 0.8 Hz), 6.51-6.53 (m, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 3.5-3.7 (bm, 1H), 2.6-3.2 (bm, 3H), 0.87 (t, 3H, J = 7.2 Hz), 0.85 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.4, 161.9, 158.1, 152.7, 148.5, 145.0, 132.7, 130.7, 121.2, 118.2 104.9, 98.9, 55.94, 55.89, 42.7, 38.7, 14.0, 12.5; LRMS *m/z* (rel. intensity %) 314 (M^+, 90), 313 (92); 283 (53), 242, (47), 227 (63), 191 (100); HRMS calcd for $C_{18}H_{23}N_2O_3$ (M+H) 315.1709, found 315.1716.

***N,N*-Diethyl-3-(4-methoxyphenyl)isonicotinamide (2.354j)**



Prepared according to General Procedure B from **2.263c** (2.8 mmol, 0.47 mL) and 4-bromoanisole (0.576 g, 3.08 mmol). Flash chromatography (CH_2Cl_2/MeOH 19.5/0.5) followed by *in vacuo* distillation (150 °C/0.9 mmHg) gave 0.60 g of (2.1 mmol, 75%) of **2.354j** as a colourless solid, mp 76-78 °C (hexanes/EtOAc); IR (KBr) ν_{max}: 3464, 1623, 1252; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.63 (s, 1H), 8.56 (d, 1H, J = 5.2 Hz), 7.41 (d, 2H, J = 8.8 Hz), 7.21 (dd, 1H, J = 4.8, 0.8 Hz), 6.95 (d, 2H, J = 8.8 Hz), 3.82 (s, 3H), 3.67 (bs, 1H), 3.10 (bs, 1H), 2.88 (bs, 1H), 2.72 (bs, 1H), 0.97 (t, 3H, J = 7.2 Hz), 0.76 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 159.9, 150.0, 148.3, 143.4, 132.9, 130.1, 128.5, 121.1, 114.2, 55.3, 42.3, 38.6, 13.4, 12.1; LRMS *m/z* (rel. intensity %) 284 (M^+, 68), 283 (69), 255 (10), 213 (30), 212 (100), 184 (9), 169 (40); HRMS calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1532.

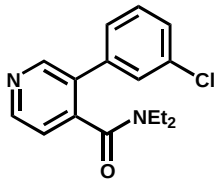
3-(4-Cyanophenyl)-*N,N*-diethylisonicotinamide (2.348b)



Prepared according to General Procedure B from **2.263c** (0.5 g, 2.8 mmol) and 4-bromo-benzonitrile (0.56 g, 3.08 mmol). Flash chromatography (CH_2Cl_2/MeOH 19.75/0.25) followed by recrystallization afforded **2.348b** (75% yield) as colourless needles, mp 112-113 °C (hexanes/EtOAc); IR (KBr) ν_{max} 3406, 2224, 1636; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, 1H, J = 5.1 Hz), 8.7 (s, 1H), 7.74 (d, 2H, J = 8.4 Hz), 7.64 (d, 2H, J = 8.8 Hz), 7.32 (s, 1H, J = 4.8 Hz), 3.70-2.70 (bm, 4H), 0.97 (t, 3H, J = 7.2 Hz), 0.84 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 150.2, 143.7, 141.0, 132.7, 131.6, 129.9, 121.2, 118.6, 112.6, 42.7, 38.9, 13.8, 12.3; LRMS *m/z* (rel. intensity %) 279 (M^+, 55), 278 (75),

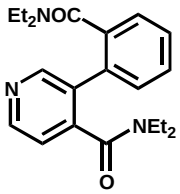
264 (3), 250 (14), 207, (100), 179 (35), 152 (32); HRMS calcd for $C_{17}H_{17}N_3O$ 279.1372, found 279.1367.

3-(3-Chlorophenyl)-*N*,*N*-diethylisonicotinamide (2.354k)



Prepared according to General Procedure B from **2.263c** (0.5 g, 2.8 mmol) and 1-bromo-3-chlorobenzene (0.59 g, 3.08 mmol). Flash chromatography (CH_2Cl_2/MeOH : 19.7/0.3) followed by recrystallization afforded **2.354k** (61% yield) as colourless needles, mp 73-75 °C (hexanes/EtOAc); IR (KBr) ν_{max} 3489, 1632; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.65-8.63 (m, 2H), 7.47-7.49 (m, 1H), 7.38-7.40 (m, 3H), 7.26 (dd, 1H, J = 4.8, 0.8 Hz), 3.60-3.90 (bm, 1H), 2.65-3.15 (bm, 3H), 0.96 (t, 3H, J = 7.2 Hz), 0.80 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 150.6, 150.0, 144.2, 138.7, 134.9, 132.3, 130.6, 129.3, 128.9, 127.8, 121.4, 43.0, 39.1, 13.9, 12.3; LRMS *m/z* (rel. intensity %) 290 (16), 289 (28), 288 (M^+, 50), 287 (65), 259 (10), 218 (31), 216 (100), 190 (10), 188 (29); HRMS calcd for $C_{16}H_{16}N_2OCl$ (M-H) 287.0951, found 287.0947.

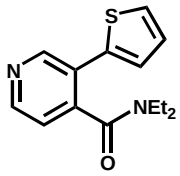
3-(2-(Diethylcarbamoyl)phenyl)-*N*,*N*-diethylisonicotinamide (2.354*l*)



Prepared according to General Procedure B from **2.263c** (0.5 g, 2.8 mmol) and *N*,*N*-diethyl-2-bromobenzamide (0.79 g, 3.08 mmol). Flash chromatography of the crude residue and recrystallization (hexanes/ Et_2O) afforded **2.354*l*** (67% yield) as colourless needles, mp 110-111 °C; IR (KBr) ν_{max} 1628; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.56 (d, 1H, J = 5.8 Hz), 8.47 (s, 1H), 7.34-7.45 (m, 4H), 7.22 (d, 1H, J =4.8 Hz), 2.80-3.90 (bm, 8H), 1.90 (t, 3H, J = 7.2 Hz), 1.04 (t, 3H, J = 7.0), 0.95 (t, 3H, J = 7.0 Hz), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (400 MHz,

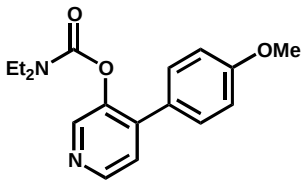
CD_2Cl_2) δ 169.9, 168.0, 150.7, 149.3, 144.9, 137.7, 134.1, 132.1, 131.3, 129.0, 128.5, 127.0, 121.4, 43.4, 43.0, 39.0, 38.9, 14.2, 14.0, 12.5, 12.4; LRMS *m/z* (rel. intensity %) 353 (54), 352 (50), 282 (25), 281 (25), 253 (11), 183 (42), 182 (100), 100 (13), 72 (35); HRMS calcd for $C_{21}H_{27}N_3O_2$ 353.2103, found 353.2099.

_N,N_-Diethyl-3-(thiophen-2-yl)isonicotinamide (2.354m)



Prepared according to General Procedure B from **2.263c** (0.5 g, 2.8 mmol) and 2-bromothiophene (0.50 g, 3.08 mmol). Flash chromatography (EtOAc/Et_3N 99/1) of the crude residue afforded **2.354m** (85% yield) as a colourless oil, IR (film) ν_{max} 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.60 (d, 1H, J = 5.2 Hz), 7.51 (dd, 1H, J = 3.2, 1.6 Hz), 7.39 (dd, 1H, J = 5.2, 3.2 Hz), 7.29 (dd, 1H, J = 5.2, 1.2 Hz), 7.24 (d, 1H, J = 5.2 Hz), 3.70 (bm, 1H), 3.20 (bs, 1H), 2.83 (m, 2H), 1.070 (t, 3H, J = 6.8 Hz), 0.76 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 149.7, 148.5, 143.1, 136.4, 128.2, 127.8, 126.4, 124.4, 121.0, 42.4, 38.7, 13.4, 12.2; LRMS *m/z* (rel. intensity %) 260 (M^+, 75), 245 (3), 231 (17), 189 (42), 188 (100), 161 (87), 160 (58); HRMS calcd for $C_{14}H_{16}N_2OS$ 260.0983, found 260.0985.

4-(4-Methoxyphenyl)pyridin-3-yl diethylcarbamate (2.354s)

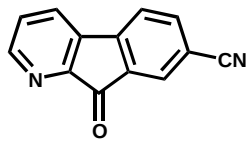


A 50 mL flame-dried round bottom flask was charged with **2.353** (0.5 g, 2.6 mmol), THF (5 mL) and $B(O^iPr)_3$ (3.1 mmol, 0.72 mL). A stock solution of LDA (4.10 mL, 2.9 mmol, 0.7M), prepared as in General Procedure A, was added to this mixture cooled to –78 °C and the reaction was allowed to reach 0 ^oC over 30 min. *N*-Methyldiethanolamine (0.37

g, 3.1 mmol) was added and the mixture was stirred for 2 h at 0 °C. After complete *in vacuo* evaporation of the solvent, in a glove-bag filled with nitrogen, $Pd(OAc)_2$ (29 mg, 0.13 mmol), S-Phos (0.107 g, 0.26 mmol), K_2CO_3 (1.10 g, 7.8 mmol), CuI (49 mg, 0.26 mmol) were added to the residue. A water condenser was fitted to the flask and 4-bromoanisole (0.32 g, 1.7 mmol) and degassed ethanol (15 mL) were added through a septum sealing at the top of the condenser. The mixture was refluxed for 3h, cooled and subjected to filtration. The solvent was evaporated to dryness and the residue, suspended in water, was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extract was washed with brine (40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of this residue by flash column chromatography (hexanes/EtOAc/MeOH 16/4/0.5) yielded **2.354s** (0.47 g, 64%) as a clear oil, IR (film) ν_{max} 1718 cm^{-1}; ^1H NMR (400.3 MHz, $CDCl_3$) δ 8.46 (m, 2H), 7.40 (d, 2H, J = 8.0 Hz), 7.30 (d, 1H, J = 4.4 Hz), 6.95 (d, 2H, J = 8.0 Hz), 3.84 (s, 3H), 3.32-3.34 (m, 4H), 1.05-1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 153.4, 146.4, 145.3, 142.1, 129.9, 127.6, 124.4, 113.9, 55.3, 42.2, 41.8, 14.0, 13.1;. LRMS *m/z* 301 (M+H, 5), 300 (29), 100 (100), 72 (37); HRMS calcd for $C_{17}H_{20}N_2O_3$ 300.1474, found 300.1413.

Synthesis of azafluorenones 2.380a-d

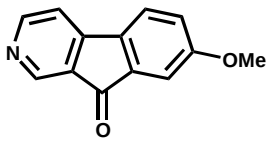
9-Oxo-9H-indeno[2,1-b]pyridine-7-carbonitrile (2.380a)



Prepared according to General Procedure C from **2.354b** (0.25 g, 0.90 mmol) in dry THF (40 mL). To this solution cooled to –78 °C, LDA (2.6 mL, 1.8 mmol) was added dropwise and the reaction mixture was allowed to reach –10 °C over 90 min, then quenched with NH_4Cl. Standard

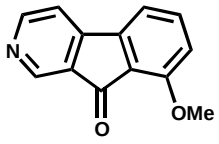
work up and flash chromatography (Hexanes/EtOAc 1/9) of the crude material yielded 102 mg of **2.380a** (55%) as a yellow solid, mp 205-207 °C (Hexanes/EtOAc); IR (KBr) ν_{max} 2230, 1729, 1612, 800, 753, 584 cm^{-1}; ^1H NMR (300. MHz, CD_3CN) δ 8.82-8.65 (m, 2H), 7.68 (d, 1H, J = 8.2 Hz), 7.54 (dd, 1H, J = 4.8, 1.0 Hz), 7.22 (d, 1H, J = 2.3 Hz), 7.15 (dd, 1H, J = 8.2, 2.3 Hz), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 152.9, 152.0, 145.1, 139.1, 138.5, 132.5, 129.0, 127.9, 127.6, 121.8, 117.6, 113.7; LRMS *m/z* (rel. intensity %) 207 (M+H, 5), 206 (100), 178 (23), 152 (14), 151 (4); HRMS calcd for $C_{13}H_6N_2O$ 206.0480, found 206.0489.

7-Methoxy-2-azafluorenone (2.380b)



Prepared according to General Procedure C from **2.354e** (0.167 g, 0.59 mmol) in dry THF (27 mL). To this solution cooled to –40 °C, LDA (2.5 mL, 1.8 mmol) was added dropwise and the reaction mixture was allowed to reach 10 °C over 2 h, then quenched with NH_4Cl. Standard work up and flash chromatography (CH_2Cl_2/MeOH 9.85/0.15) of the crude material yielded 70 mg of **2.380b** (56%) as a yellow solid, mp 153-154 °C (hexanes/EtOAc), lit. 151-153 °C (CH_2Cl_2). This compound showed spectral data consistent with those reported for the known material.

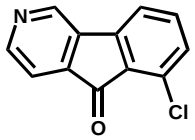
8-Methoxy-2-azafluorenone (2.380c)



Prepared according to General Procedure C from **2.354h** (0.250 g, 0.88 mmol) in 40 mL of dry THF. To this solution cooled to –40 °C LDA (3.8 mL, 2.64 mmol) was added dropwise and the reaction was allowed to reach 10 °C over 2 h, then quenched with NH_4Cl. Standard work up and flash

chromatography of the crude material (CH_2Cl_2/MeOH 9.85/0.15) yielded 115 mg of **2.380c** (63%) as a yellow solid, mp 185-186 °C (CH_2Cl_2), lit. 184-186 (CH_2Cl_2). This compound exhibits spectral data consistent with those reported for the known material.

8-Chloro-3-azafluorenone (2.380d)



Prepared according to general procedure C from **2.354k** (400 mg, 1.38 mmol) in dry THF (50 mL). To this solution cooled at −50 °C, LDA (3.0 mL, 2.1 mmol, 0.7M), was added dropwise and the reaction was stirred for 90 min at this temperature, then quenched with NH_4Cl. Standard work up and flash chromatography of the crude material (hexanes/EtOAc 6/4) yielded 0.24 g (81%) of **2.380d** as a yellow powder, mp 178-179 °C (Hexanes-EtOAc); IR (KBr) ν_{max} 3071, 1716, 1579, 1445, 1272, 783, 672; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.74 (d, 1H, J = 4.4 Hz), 7.58 (d, 1H, J = 7.8 Hz), 7.55 (d, 1H, J = 4.4 Hz), 7.49 (t, 1H, J = 7.8 Hz), 7.31 (d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 152.2, 145.1, 142.3, 139.9, 136.1, 135.8, 133.8, 131.7, 128.9, 119.6, 117.4; LRMS *m/z* (rel. intensity %) 217 (33), 215 (M^+, 100), 187 (17), 160 (13), 152 (11), 125 (10); HRMS calcd for $C_{12}H_6ClNO$ 215.0138, found 215.0133.

React IR Study for the Directed Remote Metalation Reaction of 2.354h.

A stock solution of LDA (10 mL, 1M) was prepared by addition of ^{n}BuLi (10 mmol, 4.3 mL, 2.30M) to a solution of DIPA (10 mmol, 1.4 mL) in dry THF (9.0 mL) at 0 °C. A 100 mL two-neck flask containing a very small stirring bar was fitted to the IR probe while the other neck was sealed with a rubber septum through which a temperature probe was inserted. Anhydrous THF (2.5 mL) was added to the flask and a background

spectrum was acquired at -7 °C. **2.354h** (200 mg, 0.70 mmol) dissolved in THF (0.5 mL) was injected and, after brief stirring, spectra (averages of 120 scans) were acquired every 2 min. LDA (2.1 mL, 2.1 mmol) was slowly added (ca. 0.1 mL/5 min) at -7 °C and the consumption of **2.354h** was monitored. When further additions of LDA caused no change in the amide carbonyl absorption band, ν = 1632 cm^{-1}(C=O), a few drops of ice-cold MeOH were slowly added to the mixture causing the appearance of the fluorenone (**2.380c**) carbonyl band, ν 1718 cm^{-1}. In a control experiment, the addition of THF (2.1 mL) rather than a solution of LDA in THF to substrate **2.354h** did not significantly reduce the absorption band of **2.354h**, neither did the addition of MeOH cause the appearance of relevant signals at 1718 cm^{-1}.

2.7 References

[1] a) For bioactive arylpyridines see: i) Horvath, R.F.; Zhang, L.Y.; Yoon, T.; Ping, G. U.S. Patent No. 7, 223, 778, 2007; ii) Marcoux, J.-F.; Corly, E.G.; Rossen, K.; Pye, P.; We, J.; Robbins, M.A.; Davies, I.W.; Larsen, R.D.; Reider, P.J. *Org. Lett.* **2000**, *2*, 2339-2341; iii) Zhou, X.-f.; Zhang, L.; Tseng, E.; Scott-Ramsay, E.; Schentag, J.J.; Coburn, R.A.; Morris M.E. *Drug Metab. Dispos.* **2005**, *33*, 321-328; b) For arylpyridines of agrochemical interest see: Balko *et. al.* U.S. Patent No. 6, 784,137, 2004. c) For arylpyridine of interest in material chemistry see: Grushin, V.V.; Herron, N.; LeCloux, D.D.; Marshall, W.J.; Petrov, V.A.; Wang, Y. *Chem. Commun.* **2001**, 1494-1495. Fang, A.G.; Mello, J.V.; Finney, N.S. *Org. Lett.* **2003**, *5*, 967-970.

[2] a) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* ***2001,*** 3*, 2579-2581*. Oi, S.; Fukita, S.; Inoue, S. *Chem. Commun.* **1998**, 2439-2440. b) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842-843. c) Chen, X.; Hao, X.-S.; Goodhue, C.E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790-6791. d) Imoto, S.; Uemura, T.; Kakiuchi, F.; Chatani, N. *Synlett* **2007**, 170-172. Chatani, N.; Uemura, T.; Asaumi, T.; Ie, Y.; Kakiuchi, F.; Murai, S. *Can. J. Chem.* **2005**, *83*, 755-763. e) Kakiuchi, F.; Matsumoto, M.; Tsuchiya, K.; Igi, K.; Hayamizu, T.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **2003**, *686*, 134-144.

[3] Gilman, H.; Edward, J.T. *Can. J. Chem.* **1953**, *31*, 457-468. Giam, C.-S.; Knaus, E. E. *Tetrahedron Lett.* **1971**, *52*, 4961-4964. Abramovitch, R. A.; Poulton, G. A. *J. Chem. Soc., B* **1969**, 901-903. Abramovitch, R. A.; Giam, C.-S. Giam *Can. J. Chem.* **1964**, *42*, 1627-1637. Poulton, G. A. *J. Chem. Soc., B* **1969**, 901-903.

[4] Schlecker, W.; Huth, A.; Ottow, E. *Tetrahedron* **1995**, *51*, 9531-9542.

[5] a) Katritsky, A.R.; Beltrami, H.; Sammes, M.P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2480-2484. b) Akiba, K.-y.; Iseki, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994-1999.

[6] Comins, D.L.; Abdullah, A.H. *J. Org. Chem.* **1982**, *47*, 4315-4319. Zhang, D.; Llorente, I.; Liebeskind, L.S. *J. Org. Chem.* **1997**, *62*,4330-4338.

[7] Piers, E.; Soucy, M. *Can. J. Chem.* **1974**, *52*, 3563-3564.

[8] Shiao, M.-J.; Liu, K.-H.; Lin, L.-G. *Synlett* **1992**, 655-656.

[9] Bergen, T.J,; Kellogg, R.M. *J. Org. Chem.* **1971**, *36*, 1705-1708.

[10] Corey, E.J.; Tian, Y. *Org. Lett.* **2005**, *7*, 5535-5537.

[11] Pal, M.; Batchu, V.R.; Dager, I.; Kumara Swamy, N. Padakanti, S. *J. Org. Chem.* **2005**, *70*, 2376-2379

[12] Abramovitch, R.A.; Shinkai, I. *J. Am. Chem. Soc.* **1974**, *96*, 5265-5267.

[13] Liu, Z.; Larock, R.C. *Org. Lett.* **2004**, *6*, 99-102.

[14] Raminelli, C.; Liu, Z.; Larock, R.C. *J. Org. Chem.* **2006**, *71*, 4689-4691.

[15] For a comprehensive review, see Spitzner, S. in *Science of Synthesis,* Black, D. St. C.; Ed.; Thieme, Stuttgart, **2004**, Vol. 15, pp 211-284.

[16] Thomas, A.D.; Asokan, C.V. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2583-2587

[17] Jutz, C.; Mueller, W.; Mueller. E. *Chem. Ber.* **1966**, *99*, 2479.

[18] Zolfigol, M.A.; Shirini, F.; Choghamarani, A. G.; Mohammadpoor-Baltork, I. *Green Chem*. **2002**, *4,* 562-564. Pfister, J.R. *Synthesis*, **1990**, 689-690. Cheng, D.-P.; Chen, Z.-C. *Synth. Commun.* **2002**, *32*, 793-798. Mashraqui, S.H.; Karnik, M.A. *Tetrahedron Lett.* **1998**, *39*, 4895-4898. Memarian, H.R.; Sadeghi, M.M.; Momeni, A.R. *Synth. Commun.* **2001**, *31*, 2241-2244.

[19] Hantzsch, A. *Liebigs Ann. Chem.* **1882**, *215*, 1-82.

[20] Kröhnke, F. *Synthesis* **1976**, 1-64.

[21] Kelly, T.R.; Liu, H.-t. *J. Am. Chem. Soc.* **1985**, *107*, 4998-4999.

[22] Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265-2272.

[23] Cave, G.W.V.; Raston, C.L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3258-3264.

[24] Weller, D.D.; Luellen, G.R.; Weller, D.L. *J. Org. Chem.* **1982**, *47*, 4803-4806.

[25] Jagath Reddy, G.; Latha, D.; Thirupathaiah, C.; Srinivasa Rao, K. *Tetrahedron Lett.*, **2005**, *46*, 301-302.

[26] Molina, P.; Pastor, A.; Vilaplana, M.J. *Tetrahedron Lett.* **1993**, *34*, 3773-3776.

[27] Petrich, S.A.; Hicks, F.A.; Wilkinson, D.R.; Tarrant, J.G.; Bruno, S.M.; Vargas, M.; Hosein, K.N.; Gupton, J.T. *Tetraderon*, **1995**, *51*, 1575-1584.

[28] Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959-6966.

[29] Roesh, K.R.; Zhang, H.; Larock, R.C. *J. Org. Chem.* **2001**, *66*, 8042-8051.

[30] Roesh, K.R.; Larock, R.C. *J. Org. Chem.* **2001**, *66*, 412-420. Larock, R.C.; Doty, M.J.; Han, Z. *J. Org. Chem.* **1999**, *64*, 8770-8779.

[31] Varela, J.A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787-3801.

[32] Wang, C.; Wang, Z.; Liu, L.; Wang, C.; Liu, G.; Xi, Z. *J. Org. Chem.* **2006**, *71*, 8565-8571.

[33] Dehlinger, V.; Cordier, F.; Dell, C.P.; Dreyfus, N.; Jenkins, N.; Sanderson, A.J.; Smith, C.W. *Tetrahedron Lett.* **2006**, *47*, 8973-8976. Tamagnan, G.; Alagille, D.; Fu, X.; Kula, N.S.; Baldessaarini, R.J.; Innis, R.B.; Baldwin, R.M. Thomas, S.A. *et al. Bioorg. Med. Chem. Lett.* **2006**, *16*, 3740-3744. Jiang, T. *et al. Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109-2112.

[34] Guram, A.S.; King, A.O.; Allen, J.G.; Wang, X.; Schenkel,.L.B.; Chan, J.; Bunel, E.E.; Faul, M.M.; Larsen, R.D.; Martinelli, M.J.; Reider, P.J. *Org. Lett.* **2006**, *8*, 1787-1789. Kulkarni, S.S.; Newman, A.H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2074-2079.

Knutsen, L.J.S. *et al. Bioorg. Med. Chem. Lett.* **2007**, *17*, 662-667. Blachut, D.; Czarnocki, Z.; Wojtasiewicz, K. *Synthesis* **2006**, 2855-2864.

[35] Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron Lett.* **2006**, *62*, 7521-7533. Milne, J.E.; Buchwald, S.L. *J. Am. Chem. Soc.* **2004**, *126*, 13028-13032. Kuroboshi, M.; Mizuno, K.; Kanie, K.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 563-566.

[36] Parmentier, M.; Gros, P.; Fort, Y. *Tetrahedron* **2005**, *3261-3269.* Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron* **2002**, *58*, 4429-4438 and *Tetrahedron Lett.* **2001**, *42*, 5717-5719.

[37] Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2006**, *348*, 945-952. DeShong, P.; Handy, C.J.; Mowery, M.E. *Pure Appl. Chem.* **2000**, *72*, 1655-1658. Wolf, C.; Lerebours, R.; Tanzini, E.H. *Synthesis* **2003**, *1*, 2069-2073.

[38] Pena, M.A.; Pérez Sestelo, J.; Sarandeses, L.A. *J. Org. Chem.* **2007**, *72*, 1271-1275.

[39] Due to their low toxicity, boronic acids find applications in biology and medicinal chemistry, see Yang, W.; Gao, X.; Wang, B. in Boronic Acids: Preparation and Applications in Organic Chemistry and Medicine, Hall, D. G.; Ed.; Wiley, New York. 2005, pp. 481-512. For example, Velcade® (bortezomib), a boronic acid-based proteosome inhibitor has been approved by the FDA for the treatment of multiple myeloma.

[40] Wakabayashi, S.; Kato, Y.; Mochizuki, K.; Suzuki, R.; Matsumoto, M.; Sugihara, Y.; Shimizu, M. *J. Org. Chem.* **2007**, *72*, 744-749. Lewis, R.T. *et al. J. Med. Chem.* **2006**, *49*, 2600-2610. Mudadu, M.S.; Singh, A.; Thummel, R.P. *J. Org. Chem.* **2006**, *71*, 7611-7617.

[41] Gong, L.-Z.; Knochel, P. *Synlett*, **2005**, 267-270. Wang, B. *et. al. Bioorg. Med. Chem.* **2004**, *12*, 17-21. Bunlaksananusorn, T.; Perez Luna, A.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240-2242. Karig, G.; Thasana, N.; Gallagher, T. *Synlett*, **2002**, 808-810. .

[42] Boully, L.; Darabantu, M.; Turck, A.; Ple, N. *J. Heterocycl. Chem.* **2005**, *42*, 1423-1428. Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Queginer, G. *Synlett* **2002**, 1008-1010.

[43] Although the cross coupling of arylindium reagents is relatively new, the 2-methoxy pyridine-3-ylindium reagent has been shown to cross couple in good yields. See ref. 38.

[44] The 2-pyridylboronic acid and its methyl ester were found highly susceptible of hydrolytic protodeboronation: see: Miyaura, N. *Adv. Met.-Org. Chem.* **1998**, *6*, 187-243. Isolation of 2-pyridylboronic acid, unlike for its 3- and 4-isomers failed, see: F. C.; Havinga, E. *Recl .Trav. Chim. Pays-Bas* **1965**, *84*, 439-440 and **1974**, *93*, 21-24.

[45] Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58-61. Seganish, W.M.; DeShong, P. *Org. Lett.* **2004***, 69*, 1137-1143.

[46] Pierrat, P.; Gros, P.; Fort, Y. *Org. Lett.* **2005**, *7*, 697-700.

[47] Manoso, A.S.; Ahn, C.; Soheili, A.; Handy, C.J.; Correia, R.; Seganish, W.M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 8305-8314.

[48] Zhang, N.; Thomas, L.; Wu, B. *J. Org. Chem.* **2001**, *66*, 1500-1502. Hicthcock, S.A.; Mayhugh, D.R.; Stuart Gregory, G. *Tetrahedorn Lett.* **1995**, *36*, 9085-9088.

[49] Tilley, J.W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386-390.

[50] Kelly, T.R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623-4633.

[51] Gosmini, C.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron. Lett.* **2000**, *41*, 5039-5042. Gosmini, C.; Lasry, S.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron* **1998**, *54*, 1289-1298.

[52] Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020-18021.

[53] Brandsma, L.; Verkruijsse, H.D. *Preparative polar organometallic chemistry*, Vol. 1, Springer, Berlin, 1987, p. 119.

[54] Bakker, W. I.; Wong, P.; L.; Snieckus, V.; Warrington, J. M.; Barrioult, L. in *Encyclopedia of Reagents for Organic Synthesis*, Wiley, New York, **2004**, on line publication.

[55] Campbell, M.; Snieckus, V.; Baxter, W. in *Encyclopedia of Reagents for Organic Synthesis*, Wiley, New York, **2008**, on line publication.

[56] Radinov, R.; Chanev, C; Haimova, M.J. *J. Org. Chem.* **1991**, *56*, 4793-4796.

[57] Chambers, R.D.; Hall, C.W.; Hutchinson, J.; Millar, R.W. *J. Chem. Soc., Perkin 1* **1998**, 1705-1713.

[58] Pierrat, P.; Gros, P.; Fort, Y. *Synlett* **2004**, 2319-2322.

[59] a) Khanapure, S.P.; Blehl, E.R. *Heterocycles* **1990**, *31*, 505-516. b)Trécourt, F.; Mallet, M.; Mongin, M.; Quéguiner, G. *J. Org. Chem.* **1994**, *59*, 6173-6178. c) Trécourt, F.; Mallet, M.; Mongin, M.; Gervais, B.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 8373-8380. d) Bertini, V.; Lucchesini, F.; Pocci, M.; De Munno, A. *Heterocycles* **1995**, *41*, 675-688.

[60] Zoltewicz, J.A.; Grahe, G.; Smith, C.L. *J. Am. Chem. Soc.* **1969**, *91*, 5501-5505.

[61] Zoltewicz, J.A.; Smith, C. L. *J. Am. Chem. Chem.* **1967**, *89*, 3358-3359.

[62] Tupitsyn, I.F.; Seminova, N.K. *Tr. Gos. Inst. Prikl. Khim.* **1962**, *49*, 120-126.

[63] Zoltewicz, J.A.; Smith, C. L. *Tetrahedron* **1969**, *25*, 4331-4337.

[64] Kauffmann, Th. *Angew. Chem. Int. Ed.* **1965**, *4*, 543-557.

[65] Bak, B.; Hansen, L.; Rastrup-Andersen, J. *J. Chem. Phys.* **1954**, *22*, 2013-2017.

[66] Sharma, S.D.; Doraiswamy, S. *J. Mol. Spectrosc.* **1976**, *59*, 216.

[67] Gilman, H.; Gorsich, R.D. *J. Am. Chem. Soc.* **1956**, *78*, 2217-2222.

[68] Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocl. Chem.* **1991**, *52*, 187-304.

[69] Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059-4090.

[70] Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376-393.

[71] a) Güngör, T.; Marsais, F.; Quéguiner, G. *J. Organom. Chem.* **1981**, *215*, 139-150. b) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P.R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323-3328.

[72] Bobbio, C.; Schlosser, M. *J. Org. Chem.* **2005**, *70*, 3039-3045.

[73] Shi, G.-q.; Takagishi, S.; Schlosser, M. *Tetrahedron* **1994**, *50*, 1129-1134.

[74] Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron Lett.* **2004**, *45*, 6697-6701.

[75] Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375-3383.

[76] Fort, Y.; Gros, P.; Rodriguez, A.L. *Tetrahedron Asymmetry* **2001**, *12*, 2631-2635.

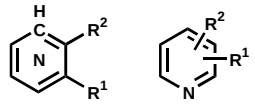
[77] Douhdou, A.; Gros, P.C.; Fort, Y.; Woltermann, C. *Tetrahedron* **2006**, *62*, 6166-6171.

[78] a) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009-2021. b) Bouillon, A.; Lancelot, J.-C.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369-4373.

[79] The positional reactivity order measured for the H-D exchange in pyridine *N*-oxide and the *N*-methylpyridinium ion is in fact *ortho* >> *meta* > *para*. See Zoltewicz, J.A.; Kauffman, G.M.; Smith, C.L. *J. Am. Chem. Soc.* **1968**, *90*, 5939-5940.

[80] Emerson, K.M.; Wilson, R.; Ashwood, M.S.; Kennedy, D.J.; Hands, D.; Brands, K.M.J.; Cottrell, I.F.; Dolling, U.-H *Synth. Commun.* **2003**, *24*, 4235-4240.

[81] The general structure **A** will be used throughout Chapter 2 to replace the less informative structure **B** which does not specify the position of R^1 and R^2 with respect to each other and to the ring nitrogen. The indication of a CH unit in **A** overrules that of a N atom.



A B

[82] a) Gribble, G.W.; Saulnier, M.G. *Tetrahedron Lett.* **1980**, *21*, 4137-4140 and b) *Heterocycles* **1993**, *35*, 151-169.

[83] Trécourt, F.; Marsais, F.; Güngör, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409-2415.

[84] Mallet, M. *J. Organomet. Chem* **1991**, *406*, 49-56.

[85] Choppin, S.; Gros, P.; Fort, Y. *Org. Lett.* **2000**, *6*, 803-805.

[86] Marsais, F.; Laperdrix, B.; Güngör, T.; Mallet, M.; Quéguiner, G. *J. Chem. Res. Synop.* **1982**, 278-279.

[87] Menzel, K.; Fisher, E.L.; DiMichele, L.; Frantz, D.E.; Nelson, T; Kress, M.H. *J. Org. Chem.* **2006**, *71*, 2188-2191. For the direct cross-coupling of (2-bromo)pyridyl-3-zinc derivative see Karig, G.; Spencer, J.A; Gallagher, T. *Org. Lett.* **2001**, *3*, 835-838.

[88] Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539-3540.

[89] Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, 2450-2451.

[90] Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035-3042.

[91] Yang, X.; Luo, S.; Fang, F.; Liu, P.; Lu, Y.; He, M.; Zhai, H. *Tetrahedron* **2006**, *62*, 2240-2246.

[92] TMSCl is assumed to be somewhat compatible with ^{t}BuLi.

[93] Pierrat, P.; Gros, P.; Fort, Y. *J. Comb. Chem.* **2005**, *7*, 879-886.

[94] For reviews on this reaction see: Frohlich, J. *Prog. Heterocycl. Chem.* **1994**, *6*, 1-35 and Schürnch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046-1057.

[95] Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832-7838. See also: Saitton, S.; Kihlberg, J.; Luthman, K. *Tetrahedron* **2004**, *60*, 6113-6120.

[96] Ogilvie, K.A. M.Sc. Thesis, Queen's University, Kingston, 2006.

[97] Cochennec, C.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Synthesis* **1995**, 321-324.

[98] Lazaar, J.; Rebstock, A.-S.; Mongin, F.; Godard, A.; Trécourt, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 6723-6728.

[99] Godard, A.; Rocca, A.; Guiller, F.; Duvey, G.; Nivolier, F.; Marsais, F.; Quéguiner, G. *Can. J. Chem.* **2001**, *79*, 1754-1761.

[100] For some examples: Mallet, M.; Quéguiner, G. *Tetrahedron* **1979**, *35*, 1625-1631. Moyer, C. A. Jr.; Bunnet, J. F. *J. Am. Chem. Soc.* **1963**, *85*, 1891-1893. Stanetty, P.; Schürnch, M.; Kereiter, K.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 567-574.

[101] See refs. 52-54 in Chapter 1.

[102] Clososki, G.; Rohbogner, C.J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684. Rohbogner, C.J.; Clososki, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1503-1507.

[103] Gros, P.; Fort, Y.; Caubére, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3071-3080.

[104] Only 18.7% deuterium incorporation was detected at C_3. See ref. 106.

[105] Trécourt, F.; Mallet, M.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 1367-1371.

[106] Comins, D.; LaMunyon, D.H. *Tetrahedron Lett.* **1998**, *29*, 773-776.

[107] 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.

[108] Marsais, F.; Le Nard, G.; Quéguiner, G. *Synthesis* **1982**, 235-237.

[109] Comins, D.L.; Joseph, S.P.; Goehring, R.R. *J. Am. Chem. Soc.* **1994**, *116*, 4719-4728.

[110] Winkle, M.R.; Ronald, R.C. *J. Org. Chem.* **1982**, *47*, 2101-2106.

[111] Keaton, K.A.; Phillips, A. . *J. Am. Chem. Soc.* **2006**, *128*, 408-409. Sengupta, S.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 4267-4270.

[112] Azzouz, R.; Bischoff, L.; Fruit, C.; Marsais, F. *Synlett* **2006**, 1908-1912.

[113] Beaulieu, F.; Snieckus, V. *Synthesis* **1992**, 112-118.

[114] Miah, M.A.J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436-5438.

[115] Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066-4068.

[116] Beaulieu, F. Ph.D. Thesis, University of Waterloo, Canada, 1994.

[117] a) Güngör, T.; Marsais, F.; Quéguiner, G. *Synthesis* **1982**, 499-500. b) Turner, J.A. *J. Org. Chem.* **1983**, *48*, 3401-3408. The low yielded *ortho* formylation of 2-*N*-(pivaoylamino)pyridine (54%) has been optimized to 78% and scaled up by Merck process chemists for the synthesis of 2-amino-3-pyridinecarboxaldehyde: Rivera, N.R.; Hsiao, Y; Cowen, J.A.; McWilliams, C.; Armstrong, J.; Yasuda, N.; Hughes, D.L. *Synth. Commun.* **2001**, *31*, 1573-1579.

[118] Fishwick, C. W. G.; Storr, R. C.; Manley, P. W. *Chem. Commun.* **1984**, 1304-1305.

[119] Cho, I.-S.; Gong, L.; Muchowski, J.M. *J. Org. Chem.* **1991**, *56*, 7288-7291.

[120] Zhichkin, P.; Cillo Beer, C.M.; Rennells, W.M.; Fairfax, D.J. *Synlett* **2006**, 379-382.

[121] Davies, A.J.; Brands, K.M.J.; Cowden, C.J.; Dolling, U.-H.; Lieberman, D.R. *Tetrahedron Lett.* **2004**, *45*, 1721-1724.

[122] Venuti, M.; Stephenson, R.A.; Alvarez, R.; Bruno, J.J.; Strosberg, A.M. *J. Med. Chem.* **1988**, *31*, 2136-2145. Sato, N.; Yue, Qi. *Tetrahedron* **2003**, *59*, 5831-5836. Kelly, T.A.; Patel, U.R. *J. Org. Chem.* **1995**, *60*, 1875-1877. Spivey, A.C.; Fekner, T.; Spey, S.E.; Adams, H. *J. Org. Chem.* **1999**, *64*, 9430-9443.

[123] Scopton, A.; Kelly, T.R. *Org. Lett*. **2004**, *6*, 3869-3871.

[124] Gschwend, H. W.; Rodriguez, H. R. *Org. React* **1979**, *26*, 1.

[125] Cuperly, D.; Gros, P.; Fort, Y. *J. Org. Chem.* **2002***, 67*, 238-241.

[126] Gros, P.; Doudouh, A.; Woltermann C. *Chem. Commun.* **2006**, 2673-2674.

[127] Gros, P.; Doudouh, A.; Woltermann C. *Org. Biomol. Chem.* **2006**, 4331-4335.

[128] Fevrier, F.C.; Smith, E.D.; Comins, D.L. *Org. Lett.* **2005**, *7*, 5457-5460.

[129] Wagner F. F.; Comins, D.L. *Org. Lett.* **2006**, *8*, 3549-3552.

[130] Mongin, F.; Frécourt, F. Quéguiner, G. *Tetrahedron Lett.* **1999**, *40,* 5483-5486.

[131] Dubey, S.K.; Knaus, E.E. *Heterocycles* **1986**, *24*, 125-134. and **1984**, *22*, 1091-1093. Hauk, A.E.; Giam, C.-S. *Perkin Trans. 1* **1980**, 2070-2076 and **1984**, 2227-2231.

[132] Meyers, A.I.; Gabel, R.A. *Heterocycles* **1978**, *11*, 133-138.

[133] Meyers, A.I.; Gabel, R.A. *Tetrahedron Lett.* **1978**, *19*, 227-230.

[134] Iwamoto, K.; Chatani, N.; Murai, S. *J. Org. Chem.* **2000**, *65*, 7944-7948.

[135] Bonneau, A.-L.; Robert, N.; Hoarau, C.; Baudoin, O.; Marsais, F. *Org. Biomol. Chem.* **2007**, *5*, 175-183.

[136] Robert, N.; Bonneau, A.-L.; Hoarau, C.; Marsais, F. *Org. Lett.* **2006**, *8*, 6071-6074.

[137] Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414-8416.

[138] Hawad, H.; Bayh, O.; Hoarau, C.; Trécourt, F.; Quéguiner, G.; Marsais, F. *Tetrahedron* **2008**, *64*, 3236-3245.

[139] Epsztajn, J.; Bienek, A.; Płotka, M.W.; Suwald, K. *Tetrahedron*, **1989**, *45*, 7469-7476. Epsztajn, J.; Bienek, A.; Kowalska, J.A. *Tetrahedron* **1991**, *47*, 1697-1706. Epsztajn, J.; Bienek, A.; Brzeziński, J.Z.; Jóźwiak, A. *Tetrahedron Lett.* **1983**, *24*, 4735-4738. Nora de Souza, M.V.; Dodd, R.H. *Heterocyles* **1998**, *47*, 811-827.

[140] Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457-1460. Sammakia, T.; Hurley, T.B.; *J. Org. Chem.* **1999**, *64*, 4652-4664.

[141] a) Epsztajn, J.; Berski, Z.; Brzeziński, J.Z.; Jóźwiak, A. *Tetrahedron Lett.* **1980**, *21*, 4739-4742. b) Iwao, N.; Kuraishi, T. *Tetrahedron Lett.* **1983**, *24*, 2649-2652. c) Watanabe, W.; Shinoda, E.; Shimizu, Y.; Furukawa, S. *Tetrahedron* **1987**, *43*, 5281-5287. d) Guillier, F.; Nivoliers, F.; Bourguignon, J.; Dupas, G.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron Lett.* **1992**, *33*, 7355-7356. e) Dormoy, J.-R.; Heymes, A. *Tetrahedron* **1993**, *49*, 2885-2914.

[142] Comins, D. L. *Synlett* **1992**, 615-625 and references therein. Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1989**, *54*, 3730-3732.

[143] Comins. D.L.; Killpack, M.O. *J. Org. Chem.* **1990**, *55*, 69-73.

[144] Kelly, T.R.; Xu, W.; Sundaresan, J. *Tetrahedron* **1993**, *34*, 6173-6176.

[145] Comins, D.L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331-5334.

[146] a) Cailly, T.; Fabis, F.; Lamaître, S.; Bouillon, A.; Rault, S. *Tetrahedron Lett.* **2005**, *46*, 135-137. b) Cailly, T.; Fabis, F.; Bouillon, A.; Lamaître, S.; Sopkova, J.; de Santos, O.; Rault, S. *Synlett* **2006**, 53-56.

[147] Mansen, H.M.; Lysén, M.; Begtrup, M.; Kristensen, J.L. *Tetrahedron* **2005**, *61*, 9955-9960.

[148] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306-312.

[149] Dunbar, P.G.; Martin, A.R. *Heterocycles* **1987**, *26*, 3165-3172.

[150] Deguest, G.; Devineau, A.; Bischoff, L. Fruit, C.; Marsais, F. *Org. Lett.* **2006**, *8*, 5889-2592.

[151] Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 4883-4884.

[152] Bolitt, C.; Mioskowski, C.; Reddy, S.P.; Falk, J.R. *Synthesis* **1988**, 388-389.

[153] Spletstoser, J.T.; White, J.M.; Tunnori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* **2007**, *129*, 3408-3419.

[154] Zhao, Y.; Snieckus, V. Manuscript in preparation.

[155] Tyrrell, E.; Brookes, P. *Synlett*, **2004**, 469-483.

[156] For their structure and properties see: a) Murafuji, T.; Mouri, R.; Sugihara, Y. *Tetrahedron* **1996**, *52*, 13933-13938 and R.; Sugihara, Y.; Takakura, K.; Murafuji, T.; Miyatake, R.; Nakasuji, K.; Kato, M.; Yano, S. *J. Org. Chem.* **1996**, *61*, 6829-6834. b) For the coupling of diethyl(4-pyridyl)borane see: Ikeda, A.; Udzu, H.; Yoshimura, M.; Shinkai, S. *Tetrahedron* **2000**, *56*, 1825-1832 and Hirata, O.; Yamamoto, M.; Sugiyasu, K.; Kubo, Y.; Ikeda, M.; Takeuchi, M.; Shinkai, S. *J. Supramol. Chem.* **2002**, *2*, 133-142; c) for large scale coupling of diethyl(3-pyridyl)borane see: Wei, H.; Sudini, R.; Yin, H. *Org. Process Res. Dev*., **2004**, *8*, 955-957. Lipton, M.F.; Mauragis, M.A.; Maloney, M.T.; Veley, M.F.; VanderBor, D.W.; Newby, J.J.; Appell, R.B.; Daugs, E. *Org. Process Res. Dev*., **2003**, *7*, 385-392.

[157] Khashin, E.; Zavalij, P.Y.; Vedemikov, A.N. *J. Am. Chem. Soc.* **2006**, *128*, 13054-13055.

[158] Baker, S.J.; Zhang, Y.-K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M.R.K.; Sanders, V.; Plattner, J.J. *J. Med. Chem.* **2006**, *49*, 4447-4450. Baker, S.J.; Akama, T.; Zhang, Y.-K., Sauro, V.; Singh, R.; Kully, M.; Khan, J.; Plattner, J.J.; Benkovic, S.J.; Lee, V.; Maples, K.R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5963-5967.

[159] Beletskaya, I.P.; Bregadze, V.I.; Ivushkin, V.A.; Petrovskii, P.V.; Sivaev, I.B.; Sjöberg, S.; Zhigareva, G.G. *J. Organomet. Chem.* **2004**, *689*, 2920-2929.

[160] Voisin, A.S.; Bouillon, A.; Lancelot, J.-C.; Lesnard, A.; Oulyadi, H.; Rault, S. *Tetrahedron Lett.* **2006**, *47*, 2165-2169.

[161] a) Hodgson, P.; Salingue, F. *Tetrahedron Lett.* **2004**, *45*, 685-687 and b) Boulton, L. T.; Crook, R. J.; Pettman, A. J.; Walton, R., Pfizer Global R & D. Sándwich, Kent, UK, U.S. Patent No. 7,026,479.

[162] Matondo, H.; Souirti, S.; Baboulene, M. *Synth. Commun.* **2003**, *33*, 795-800.

[163] Khlobystov, A.N.; Brett, M.T.; Blake, A.J.; Champness, N.R.; Gill, P.M.W.; O'Neill, D.P.; Teat, S.J.; Wilson, C.; Schröder, M. *J. Am Chem.Soc.* **2003**, *125*, 6753-6761. Fernando, S.R.L.; Maharoof, U.S.M.; Deshayes, K.D.; Kinstle, T.H.; Ogawa, M.Y. *J. Am. Chem. Soc.* **1996**, *118*, 5783-5790.

[164] Combiphos, Inc. and several other fine chemical suppliers have enlisted it in their catalogues.

[165] Oda, M.; Ogura, K.; Thanh, N. C.; Kishi, S.; Kuroda, S.; Fujimori, K.; Noda, T.; Abe, N. *Tetrahedron Lett.* **2007**, *48*, 4471-4475.

[166] 3- and 4-pyridineboronic acids (and corresponding esters) are available in mg to gram quantities from numerous suppliers; *e.g.*, Aldrich Chemical Company, Inc., Milwaukee,

WI, USA, Frontier Scientific, Inc., Logan, Utah, USA, Lancaster Synthesis, Inc., Windham, NH, USA.

[167] (a) Li, W.; Nelson, D.P.; Jensen, M.S.; Hoerrner, R.S.; Dongwei, C.; Larsen, R.D. *Org. Syn.* **2005**, *81*, 89-92 and *Org. Lett.* **2003**, *5*, 4835-4837; (b) Li, W.; Nelson, D.P.; Jensen, M.S.; Hoerrner, R.S.; Cai, D.; Larsen, R.D.; Reider, P.J. *J. Org. Chem.* **2002**, *67*, 5394-5397. Subsequently, 3-pyridylboroxin has been used directly in Suzuki couplings; see: (c) Cioffi, C.L.; Spencer, W.T.; Richards, J.J.; Herr, R.J. *J. Org. Chem.* **2004**, *69*, 2210-2212.

[168] For the preparation and coupling of 3-pyridyl tetrabutylammonium trifluoroborates, see: (a) Batey, R.A.; Quach, T.D. *Tetrahedron Lett*. **2001**, *42*, 9099-9103.. For coupling of 3-pyridyl potassium trifluoroborate with 5-bromopyrimidine, see: (b) Molander, G.A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302-4314. For coupling of 3-pyridyl potassium trifluoroborate with aryl chlorides, see: (c) Barder, T.E.; Buchwald, S.L. *Org. Lett.* **2004**, *6*, 2649-2652.

[169] Coudret, C. *Synth. Commun.* **1996**, *26*, 3543-3547.

[170] (a) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885-2890. (b) Bouillon, A.; Lancelot, J.-C.; Sopkova, J.; de Santos, O.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043-10049. c) Voisin, A.-S.; Bouillon, A.; Berenguer, I.; Lancelot, J.-C.; Lesnard, A.; Rault, S. *Tetrahedron* **2006**, *62*, 11734-11739.

[171] (a) Parry, P. R.; Bryce, M. R.; Tarbit, B.; *Synthesis* **2003**, *7*, 1035-1038. (b) Parry, P.R.; Wang, C.; Batsanov, A.S.; Bryce, M.R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541-7543. For cross coupling of these boronic acids see: (c) Thompson, .A.E.; Hughes, G.; Batsanov, A.S.; Bryce, M.R.; Parry, P.R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388-390. (d) Thompson, A.E.; Batsanov, A.S.; Bryce, M.R.; Saygili, N.; Parry, P.R.; Tarbit, B. *Tetrahedron* **2005**, *61*, 5131-5135. (e) Saygili, N.; Batsanov, A.S.; Bryce, M.R. *Org. Biomol. Chem.* **2004**, *2*, 852-857.

[172] a) Durrant, S.J. *et al. Heterocycles* **2006**, *70*, 509-517. b) Wiles, J.A. *et al. Bioorg, Med. Chem. Lett.* **2006**, *16*, 1277-1281.

[173] a) Ishiyama, T.; Takagi, J.; Nobuta, Y.; Miyaura, N. *Org. Syn.* **2005**, *82*, 126-131. b) Chotana, G.A.; Rak, M.A.; Smith III, M.R. *J. Am. Chem. Soc.* **2005**, *127*, 10539-10544. c) Cho, J.-Y.; Tse, M.K.; Holmes, D.; Maleczka, R.E.; Smith III, M.R. *Science* **2002**, *295*, 305-308. d) Mkhalid, I.A.I.; Coventry, D.; Albesa-Jove, D.; Batsanov, A.S.; Howard, J.A.K.; Perutz, R.N.; Marder, T.B. *Angew. Chem. Int. Ed.* **2006,** *45,* 489-491. e) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett*. **2002**, *43*, 5649-5651.

[174] Upton, C.J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094-1098.

[175] Beak, P.; Farney, R. *J. Am. Chem. Soc.* **1973,** *95*, 4771-4772.

[176] Krizan, T.D.; Martin, J.C. *J. Am. Chem. Soc.* **1983,** *105*, 6155-6157.

[177] Caron, S.; Hawkins, J.M. *J. Org. Chem.* **1998**, *63*, 2054-2055.

[178] Larkin, A.L. M.Sc. Thesis, Queen's University, Kingston, ON, Canada, 2002.

[179] Recently, a similar one-pot protocol for the hydroxylation of halopyridines has been reportes, see: Voisin, A.S.; Bouillon, A.; Lancelot, J.-C.; Rault, S. *Tetrahedron* **2005**, *61*, 1417-1421.

[180] Green, L.A.. M.Sc. Thesis, Queen's University, Kingston, Canada, 2001.

[181] For some examples see: Tomoya, H.; Kenichi, H.; Hiroyuki, K. *Org. Lett.* **2007**, *9*, 1315-1318.

[182] Hawthorne, M. F. *J. Org. Chem.* **1958**, *23*, 1579-1580. Letsinger, R. L.; Skoog, I. *J. Am. Chem. Soc.* **1955**, *77*, 2491-2494.

[183] a) Anctil, E.; Snieckus, V. in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Mejere, A.; Diederich, F. Eds.; Wiley-VCH: Weinheim, Germany, 2004: Vol. 2, pp 761-813. (b) Anctil, E.J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150-160.

[184] a) Maddaford, S.P.; Keay, B.A. *J. Org. Chem.* **1994**, *59*, 6501-6503. b) Andersen, N.G.; Maddaford, S.P.; Keay, B.A. *J. Org. Chem.* **1996**, *61*, 9556-9559. c) Cristofoli, W.A.; Keay, B.A *Tetrahedron Lett.* **1991**, *32*, 5881-5884.

[185] O'Neill, B.T.; Yohannes, D.; Bundesmann, M.W.; Arnold, E.P. *Org. Lett.* **2000**, *2*, 4201-4204.

[186] This extensive screening was completed with the generous collaboration of Kevin A. Ogilvie, Sunny Lai and Simon Lopez whose contributions are footnoted in Table 2.9. With one exception (entry 14), aromatic halides were tested.

[187] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

[188] Marsais, M.; Breant, P.; Ginguene, A.; Quéguiner, G. *J. Organomet. Chem.*, **1981**, *216*, 139-147.

[189] Nitro groups are not known to interfere with Suzuki-Miyaura coupling, see for examples: Jing, L.; Fitzgerald, A. E.; Neelakandha, N. S. *J. Org. Chem.* **2008**, *73*, 2951-2954; Yasunori, Y.; Miho, T.; Xiao-Qiang, Y.; Miyaura, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 928-931.

[190] Polystyrene-supported diethanolamine: Gros, P.; Doudouh, A.; Fort, Y. *Tetrahedron Lett.* **2004**, *45*, 6239-6241.

[191] Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Synth. Commun.* **1998**, *28*, 2071-2075.

[192] Prostakov, N.S.; Soldatenkov, A.T.; Kolyadina, N.M.; Obynochnyi, A.A. *Russ. Chem. Rev.* **1997**, *66*, 121-138.

[193] Wu, Y.-C. *Heterocycles* **1989**, *29*, 463-475.

[194] Fu, J.-m.; Zhao, B.-p.; Sharp, M.J.; Snieckus, J. *J. Org. Chem.* **1991**, *56*, 1683-1685.

[195] a) Rebstock, A.-S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Org. Biomol. Chem.* **2004**, *2*, 291-295. b) For substituted cases see: Epsztajn J.; Jóźwiak, A.; Krysiak, J.K.; Łucka, D. *Tetrahedron* **1996,** *52*, 11025-11036.

[196] Familoni, O.B. Ionica, I.; Bower, J.F.; Snieckus, V. *Synlett*, **1997**, 1081-1083.

[197] Rebstock, A.-S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron* **2003**, *59*, 4973-4977.

[198] Tilly, D.; Castanet, A.-S.; Mortier, J. *Tetrahedron Lett.* **2006**, *47*, 1121-1123.

[199] McCubbin, A.J.; Snieckus, V.; Lemieux, R.P. *Liq. Cryst.* **2005**, *32*, 1195-1203.

[200] a) Fu, J.-m. Ph.D. Thesis, University of Waterloo, Canada, 1990; b) Tilly, D.; Castanet, A.-S.; Mortier, J. Unpublished results. c) Fu, J.-m.; White, C.; Zhao, B.-p. Unpublished results.

[201] Rebstock, A.-S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron* **2004**, *60*, 2181-2186.

[202] The addition of lithium morpholide to cyano-azabiaryls has been used in the synthesis of azaphenanthridines, see ref. 147. Furthermore, the DoM of cyanopyridines and benzonitriles requires 1.5 to 2.0 equivalents of LiTMP, see: refs 146, 147 and Kristensen, J.; Lysén M.; Vedso, P.; Megtrup, M. *Org. Lett.* **2001**, *3*, 1435-1437.

[203] Sibi, P.M.; Chattopadhyay, S. Dankwardt, J. W.; Snieckus, V. *J. Am. Chem. Soc.* **1985**, *107*, 6312-6315. Mills, R.J.; Taylor, N.J. and Snieckus, V. *J. Org. Chem*. **1989**, *54*, 4372-4385. Butenschoen, H.; Winkler, M.; Vollhardt, K. P. C. *Chem. Commun.* **1986**, 388-390. MacNeil, S. L.; Wilson, B. J.; Snieckus, V. *Org. Lett.* **2006**, *8*, 1133-1136. Ciske, F.L.; Jones Jr., W.D. *Synthesis* **1998**, 1195-1198.

[204] Shiao, M.-J.; Peng, C.-Y.; Wang, J.-S.; Ma, Y.-T. *J. Chin. Chem. Soc.* **1992**, *39*, 173-176.

[205] Olah, G. A. *Friedel-Crafts Chemistry*, Wiley, New York, **1973**.

[206] Zhao, Z.; Jaworski, A.; Piel, I.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2617-2620.

[207] For the preparation and characterization of **2.354e-g** and **2.354n-r** see ref. 96.

CHAPTER 3

Studies Towards the Synthesis of Isoprekinamycin

3.1 The Kinamycin Antibiotics

The Kinamycins (**3.4a-e,f**,**j**, Fig. 3.1) are a class of metabolic compounds (isolated from cultures of *S. murayamaensis)*, some of which strongly active against Gram-positive bacteria but all ineffective against Gram-negative bacteria.[1] Kinamycins A, C and F also show potent cell growth inhibition effects (on either Chinese hamster ovary or K562 leukemia cells) which have encouraged studies aimed at the development of structurally related anticancer agents.[2] For more than 20 years after the publication of their isolation by Omura in 1970,[3] kinamycins were believed to be cyanobenzo[*b*]carbazoles **3.1**, a structure which, although incorporating a cyano group which escaped detection by ^{13}C NMR, was supported by X-ray crystallographic studies.[3e,4] Only in 1988, during a biosynthetic study involving the feeding of $(^{15}NH_4)_2SO_4$ to the mycelium, the ^{13}C NMR spectrum of kinamycin D surrendered a very weak doublet of doublet centered at 78.5 ppm which, when compared to spectra of natural abundance kinamycin samples, brought attention to a tiny singlet, almost overlapped with the solvent signal ($CDCl_3$).[5] This signal was still some 30 ppm upfield of the values observed in simple cyanamides (110-120 ppm), and this discrepancy was attributed to unspecified electronic effects of the indoloquinone system. In 1990, during synthetic studies towards a BC ring synthon for the kinamycins, Dmitrienko obtained two *N*-cyanoindoles-4,7-diones **3.3a,b** (Fig. 3.1) whose N-CN ^{13}C NMR signals were found at ~ 104 ppm.[6] This evidence demonstrated that the anomalous shift of the N-cyano resonance obtained from kinamycins could not be ascribed to the *N*-cyano indole-dione ring system. An even stronger alarm came three

years later from Echavarren's total synthesis of **3.2**, a metabolite isolated from *S. murayamaensis* and labelled CpdA, which had been named prekinamycin because it was suspected to be a key precursor of the kinamycins. Echavarren's spectroscopic data[7] for synthetic **3.2** did not match those of CpdA, and this finding was rapidly followed in 1994 with the independent disclosure, by Dmitrienko and Gould, of the correct diazobenzo[*b*]fluorene skeleton of kinamycins (**3.4**).[8] The revised structure of prekinamycin (**3.5**) immediately became an intriguing synthetic target and, only two years later, Hauser disclosed a brief synthesis of **3.5** but with analytical details which were bound to raise more eyebrows.[9] In fact, Hauser's spectral data for **3.5** did not match those of CpdA; however, they were found to superimpose with those of another metabolite of unknown structure (named CpdB).[10]

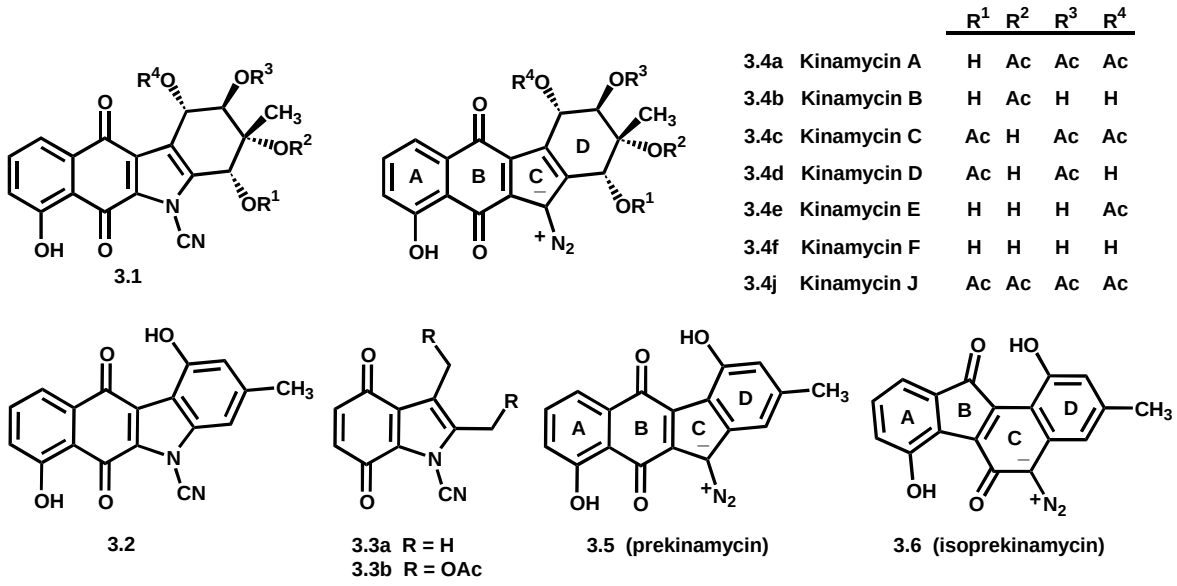


Figure 3.1 Incorrect and Revised Chemical Structures of Some Members of the Kinamycins Family and their Synthetic Models 3.3a,b

While the name "prekinamycin" and the structure **3.5** were transferred to CpdB, the true identity of CpdA became, once again, a mystery. Finally, in 2000, Dmitrienko gathered

sufficient evidence to correct the former diazobenzo[*b*]fluorene skeleton of CpdA with the angular diazobenzo[*a*]fluorene system (**3.6**) and assigned to it the name "isoprekinamycin".[11] The interest over the rare structural features of kinamycins was further heightened when, in 2001, Wyeth-Ayerst researchers disclosed the structures of Lomaiviticin A (**3.7**) and B (**3.8**), two glycosylated homodimeric diazobenzo[*b*]fluorenes (isolated from the marine actinomycete *Micromonospora lomaivitiensis*) that displayed extremely high antitumor activity against a broad range of cells (Fig. 3.2).[12] A study towards the enantioselective synthesis of the central ring system of lomaiviticin A has recently appeared.[13]

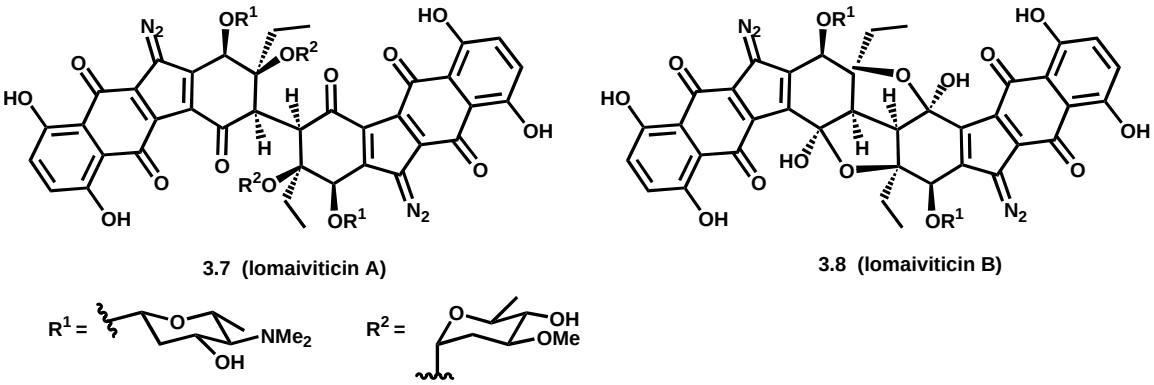
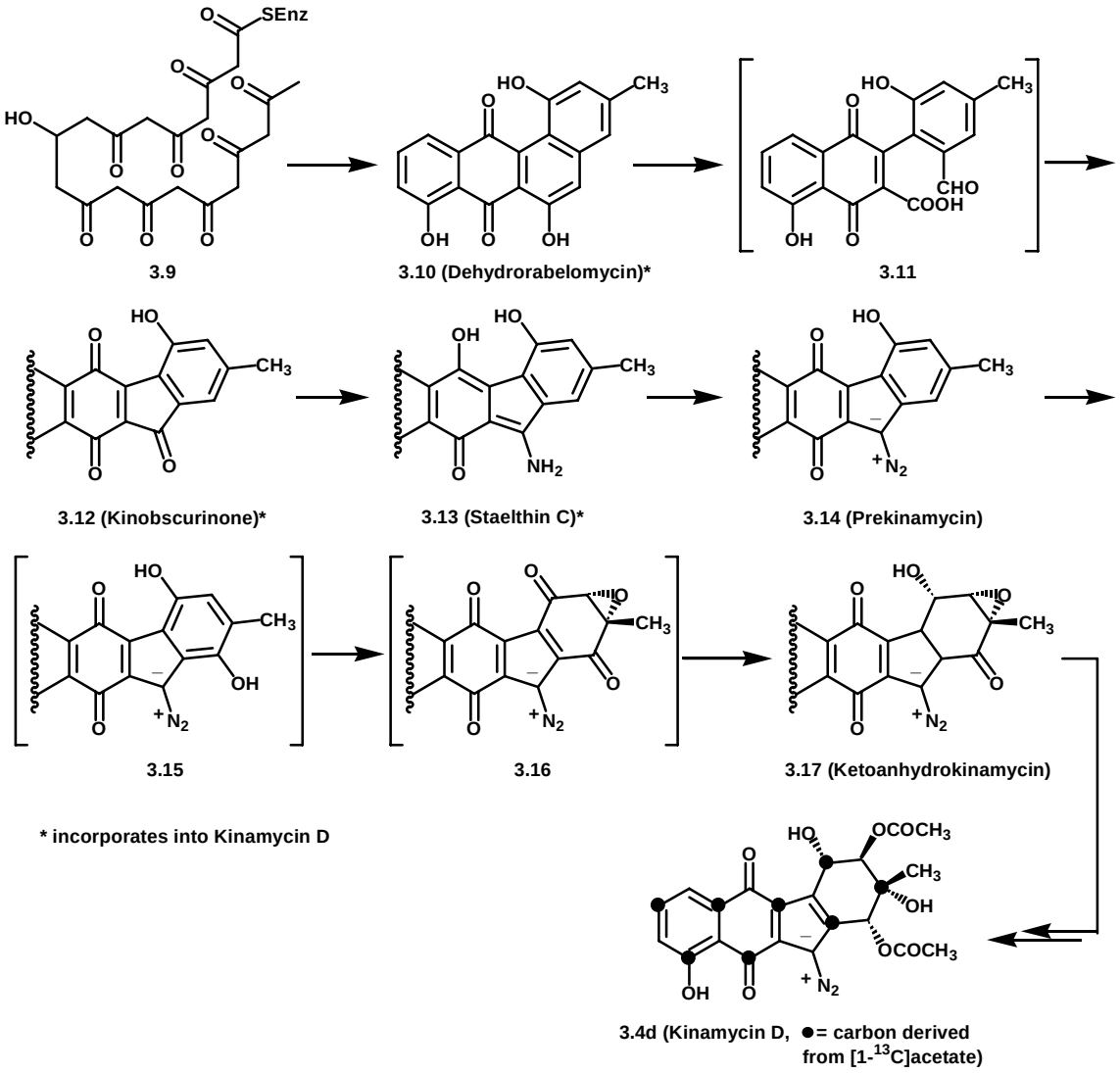


Figure 3.2 Structures of Lomaiviticin A and B

3.1.1. Biogenesis of the Kinamycins

Although most of the biosynthetic studies refer to the *N*-cyanobenzo[*b*]carbazole skeleton, the early data and conclusions can be safely transferred to the diazobenzo[*b*]fluorene frame. Separate feedings of [1-^{13}C]acetate and [2-^{13}C]acetate have secured the polyketide origin of the whole kinamycin skeleton (Scheme 3.1),[14] and the origin of the diazotized carbon has also been confirmed to be the C_2 of acetate. Among the metabolites isolated from the media of *S. murayamaensis*,

dehydrorabelomycin (**3.10**) has been shown to enter the biosynthetic pathway to kinamycin D.[15]



Scheme 3.1

Gould has suggested that cleavage of the angular ring of **3.10** may provide **3.12** as the first benzo[*b*]fluorene in the biogenetic sequence. Logical progression of the biosynthesis and the observation that both kinobscurinone (**3.12**) and stealthin C (**3.13**) are incorporated into kinamycin D, suggests the placement of the C-ring amination step at this point. The mechanism of diazotization is still a matter for speculation; however, the

presence of the diazo group in prekinamycin (**3.14**) clearly indicates that this process occurs before the dearomatization of the D ring begins. A similar oxidation sequence observed in other biosyntheses[16] suggests that the oxidation of the D ring proceeds through the formation of hydroquinone **3.15**, direct epoxidation to epoxyquinone **3.16** and its reduction to the corresponding epoxyquinol **3.17**. To our knowledge, the announced synthesis of **3.15** to experimentally support its intermediacy in the kinamycins biosynthesis has not yet been reported. Finally, brief oxygen functionality changes to **3.17** lead to kinamycin F, which is thought to be the branching point to all acetylated kinamycins.

3.1.2. Mechanism of Action of the Kinamycins

Due to the similarity of the former indoloquinone skeleton with the structure of the clinical antitumor agent mitomycin C (**3.18**, Fig. 3.3), kinamycins were initially thought to act as reductively activated DNA-alkylating agents through a mechanism similar to that of mitomycins.[17] Upon structural revision of the kinamycins, four natural products (**3.19**-**3.22**) were singled out containing the rare diazo group and displaying antitumor or/and antibiotic activity presumably based on the reactive N_2 functionality.[18]

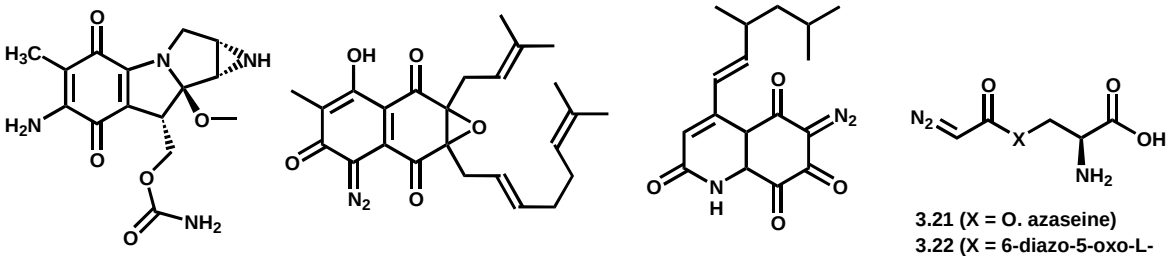
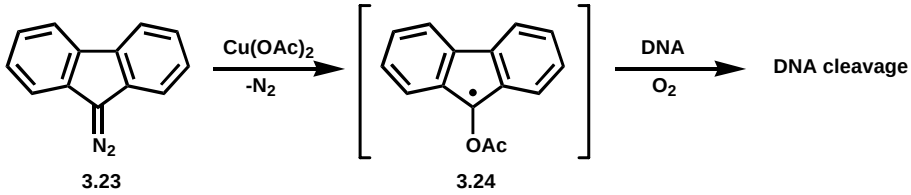


Figure 3.3 Structures of Mitomycin C and Natural Products Containing the Diazo Group

The molecular mechanism of action of kinamycins is a matter for wide discussion. Working on a simple model, Jebaratnam has found that diazofluorenone **3.23** nicks plasmid DNA upon exposure to the oxidant $Cu(OAc)_2$ and has suggested that, in the biological medium, similar events may be triggered by endogenous oxidants leading to a radical intermediate that, such as **3.24**, is capable of damaging DNA through well known oxygen mediated pathways (Scheme 3.2).[19]

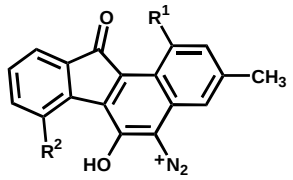


Scheme 3.2

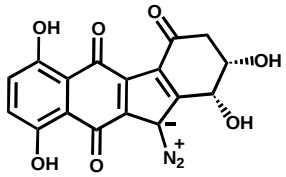
However, lomaiviticin A has been reported to be active under *reductive* conditions which are prevalent in the intracellular space.[20] Furthermore, kinamycin D and its model 1-methoxydiazofluorenone have been reported to appreciably damage the supercoiled plasmid pBR322 under thiol-promoted reductive conditions (dithiothreitol) while being ineffective in the absence of a promoter. On the contrary, kinamycin A and C have been shown to inhibit the catalytic activity of DNA topoisomerase IIα but to become ineffective in this respect when they are pretreated with dithiothreitol. This suggests that they may be targeting critical protein sulfhydryl groups present in the topoisomerase IIα. However, kinamycin A and C did not act as a topoisomerase IIa poison nor was the inhibition of the catalytic activity of this enzyme correlated to the cell growth inhibitory effects of the kinamycins. Furthermore, neither kinamycin undergoes cross-linking or intercalation processes with DNA. Collectively, these observations suggest that kinamycins may have a completely different target than that of the anticancer drugs

currently in clinical use. Dmitrienko has suggested a mechanism analogous to the reaction of aryldiazonium ions with DNA, in which the amino groups of guanine and adenine residues nucleophilically attack the diazo group and generate unstable triazenes whose decomposition to radicals is driven by loss of nitrogen. These radicals eventually combine with purine radicals to form arylpurines and, with damaged DNA, to form depurinated sites or to cleave the phosphodiester backbone.[21] To support this hypothesis, Dmitrienko ranked a number of diazo compounds, including benzo[*a*]- and [*b*]fluorenes, according to their diazonium ion character as estimated by their calculated N-N bond lengths and C-N_2 IR stretching frequencies (Scheme 3.3). This data indicated that the ionic character of the diazo group, and therefore its electrophilicity is amplified, as estimated by shorter N-N bonds and higher C-N_2 frequency, by the presence of the keto group in the B ring of benzodiazo[*a*]fluorenes and by the intramolecular H-bonding network, particularly the C_7-OH group. Indeed, the increasing diazonium ion character of isoprekinamycin, kinamycin B and lomaiviticin A (the latter mimicked by the simple model **3.27**) was found to parallel their antitumor and antibiotic activity. Furthermore, this trend of electrophilic reactivity was confirmed experimentally by the very different rates at which *β*-naphthol underwent reaction with **3.6** and **3.30** through mechanisms involving nucleophilic attack of the diazo group. While **3.6** was completely consumed in 9 hours at 0 °C, **3.30** underwent only negligible reaction unless drastic conditions were used. As noted by Feldman and Eastman, Dmitrienko's proposal does not appear to completely apply to the diazobenzo[*b*]fluorene system. In fact, in spite of its inhibited H-bond network, kinamycin J (**3.4j**) displays a higher empirical $\nu(N_2)$ value (and presumably a higher diazonium ion character) than that of kinamycin F (**3.4f**, Scheme 3.3).[22]

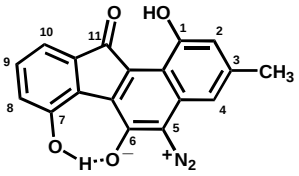
diazocompound	calc $\nu(N_2)$ (cm^{-1})	calc N-N (Å)
9-diazofluorene	1906	1.133
2,1-naphthoquinodiazide	2056	1.111
3.30	2087	1.108
3.25	2101	1.107
3.26	2125	1.105
isoprekinamycin (3.6)	2139	1.103
kinamycin B (3.4b)	2188	1.099
3.27	2212	1.097
$Ph\text{-}N_2^+ Cl^-$	2212	1.100



3.25 R^1 = OH, R^2 = H
3.26 R^1 = H, R^2 = OH

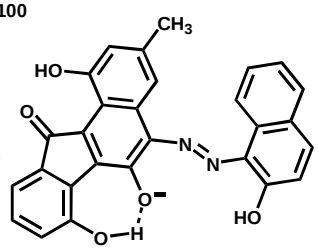


3.27



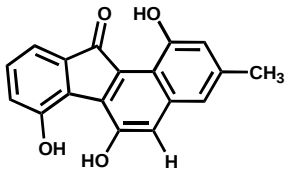
3.6 ($\nu(N_2)$ = 2162 cm^{-1})

0 °C / THF / 9h
Cs_2CO_3
β-naphthol

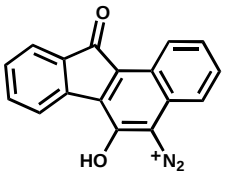


3.28 (29%)

+

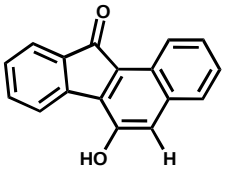


3.29 (61%)

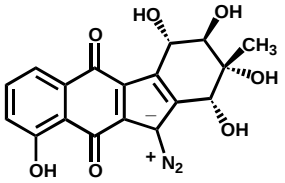


3.30 ($\nu(N_2)$ = 2105 cm^{-1})

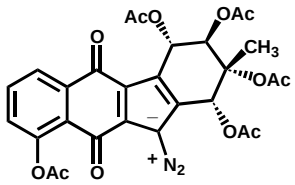
0 °C / THF / 17h
Cs_2CO_3
β-naphthol
negligible reaction
or
H_2O (pH 9)
EtOH, reflux
quant.



3.31



3.4f (Kinamycin F, $\nu(N_2)$ = 2120 cm^{-1})

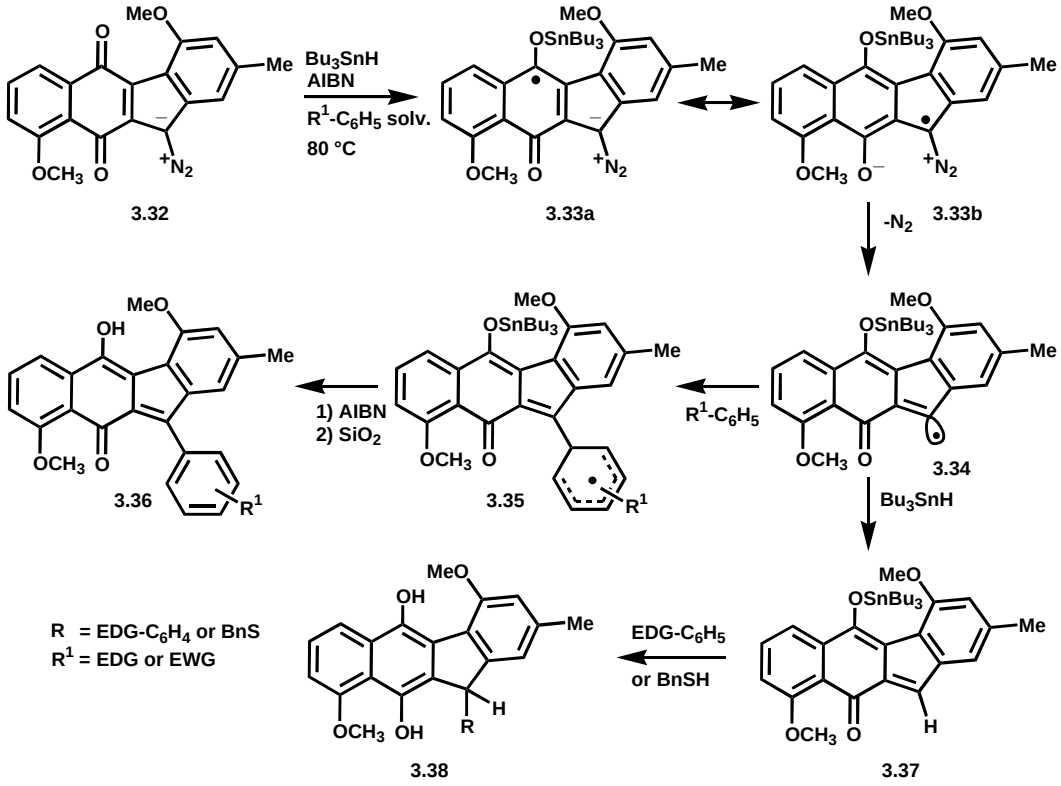


3.4j (Kinamycin J, $\nu(N_2)$ = 2150 cm^{-1})

Scheme 3.3

Feldman and Eastman have studied the reductive activation chemistry of prekinamycin and its dimethyl ether **3.32** with Bu_3Sn-H/AIBN as a model 1-electron reductant (Scheme 3.4). They proposed that nitrogen loss from the initial radical **3.33** drives the formation of the highly reactive sp^2 radical **3.34** which, in addition to the standard hydrogen abstraction from DNA, was shown to be capable of addition to electron-poor and electron-rich arenes (**3.34** → **3.35**). The orthoquinonemethide **3.37**, obtained from further 1-electron reduction of **3.34**, was proven to be a competent electrophilic partner

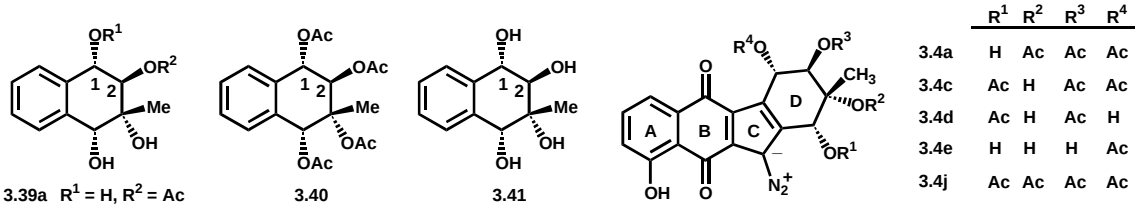
for electron-rich arenes and alkanethiols. The role of nonstannylated derivatives of **3.34** and **3.37** in the bioactivity of kinamycins remains to be demonstrated; however, this study provides an idea of the chemistry available to kinamycins under reductive conditions and hints at the possibility that diazobenzo[*b*]fluorenes may have been selected through evolutionary pressure by virtue of their ability to convert biologically accessible 1-electron reductants into the potentially lethal species **3.34** and **3.37**.



Scheme 3.4

The unusual observation that kinamycin A (**3.4a**) blocks the G_1/S cell cycle in synchronized Chinese hamster ovary cells only upon entry to a second cell cycle has suggested that kinamycin A may be slowly deacetylated to kinamycin F (**3.4f**) by intracellular esterases. This observation and the very close IC_{50} values of kinamycin F, A and C (0.33 μM, 0.31 μM and 0.37 μM, respectively, for growth inhibition in K562

cells), implicate kinamycin F as a the potential bioactive growth inhibitory form of all kinamycins. Indeed, kinamycin F has been recently subjected to a deeper scrutiny by Dmitrienko and Hasinoff with particular attention to the effect of glutathione (GSH) on its cytotoxicity.[23] GSH was found to dramatically increase the *in vitro* nicking of pBR322 plasmid DNA by kinamycin F. However, the significant DNA damage in K562 cells observed even with micromolar concentrations of kinamycin F was not affected by GSH depletion or supplementation. Based on NMR measurements, computational support and comparisons with synthetic models of the highly oxygenated D-ring of kinamycin F, Dmitrienko has also concluded that the preferred conformation of kinamycin F is unlike that of all the other kinamycins.[24] To illustrate, the ^{1}H NMR spectra of **3.39a,b** and **3.40** (Fig. 3.4), as well as those of kinamycins A, C, D, E (**3.4a,c-e**) and kinamycin J (**3.4j**) for which **3.40** is a simplified structural model, display values of $J_{1,2}$ (6.8-8.3 Hz) consistent with the predominance, in each case, of a half-chair conformation of the D ring, in which C_1- and C_2-hydroxy or acetoxy groups are in pseudoequatorial orientations.



3.39a R^1 = H, R^2 = Ac
3.39b R^1 = Ac, R^2 = H

3.40

3.41

	R^1	R^2	R^3	R^4
3.4a	H	Ac	Ac	Ac
3.4c	Ac	H	Ac	Ac
3.4d	Ac	H	Ac	H
3.4e	H	H	H	Ac
3.4j	Ac	Ac	Ac	Ac

Figure 3.4 Synthetic Models of the D Ring of Kinamycins

However, unlike its tetrol model **3.41** which exhibits a similar half-chair conformation with $J_{1,2}$ = 6.8 Hz, kinamycin F has a $J_{1,2}$ of 2.7 Hz, and therefore suggests a different conformational preference compared to the other known kinamycins. In fact, *ab initio* molecular orbital calculations suggest that kinamycin F prefers to adopt a half-chair

conformation (favored by 0.4 Kcal/mol in the gas phase) in which the C_1- and C_2-hydroxy groups occupy a pseudoaxial orientation (conformation A, Fig. 3.5).

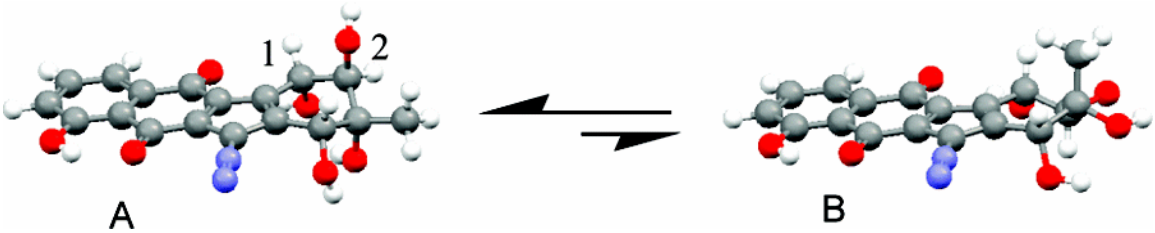


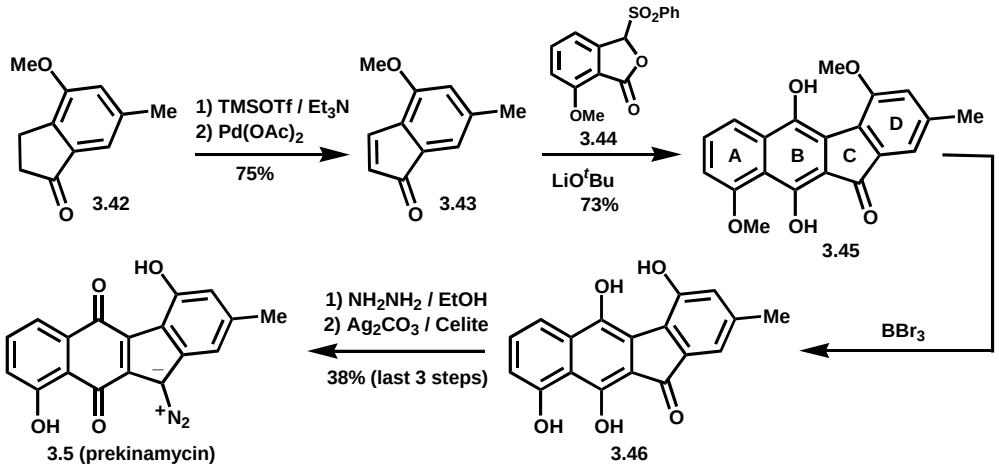
Figure 3.5. Calculated Energy Minimum Conformations of Kinamycin C (reproduced with permission of the editor)

Conformations A and B have been linked to two diazo stretches (at 2165 and 2143 cm^{-1}, respectively) present in the solution IR spectrum of kinamycin F. Ab initio calculations on simpler models suggest that the higher diazonium character of conformation A may be due to a better alignment and hence stronger through-space interaction of the oppositely polarized C-O and C-N bond dipoles. While no mechanistic implication has been drawn, this finding points at the opportunity to fine-tune the electron affinity of the diazo group of kinamycin congeners through an educated choice of their substituents.

3.1.3. Synthesis of Kinamycins and Prekinamycin

Several groups have tackled the synthesis of both the supposed benzo[*b*]carbazole and the actual benzo[*b*]fluorene skeletons of kinamycins. The first total synthesis of a kinamycin has only recently been published by Porco[25] (2006), followed by the reports of Nicolaou[26] and Ishikawa.[27] The preparations of the simpler aromatic precursor (stealthin C,[28] kinobscurinone[29] and prekinamycin, Scheme 3.1) are, instead, earlier achievements (1995-1997). The first total synthesis of prekinamycin is due to Hauser who, in a one-pot Michael addition – electrophilic condensation followed by sulfinate loss, bridged the A

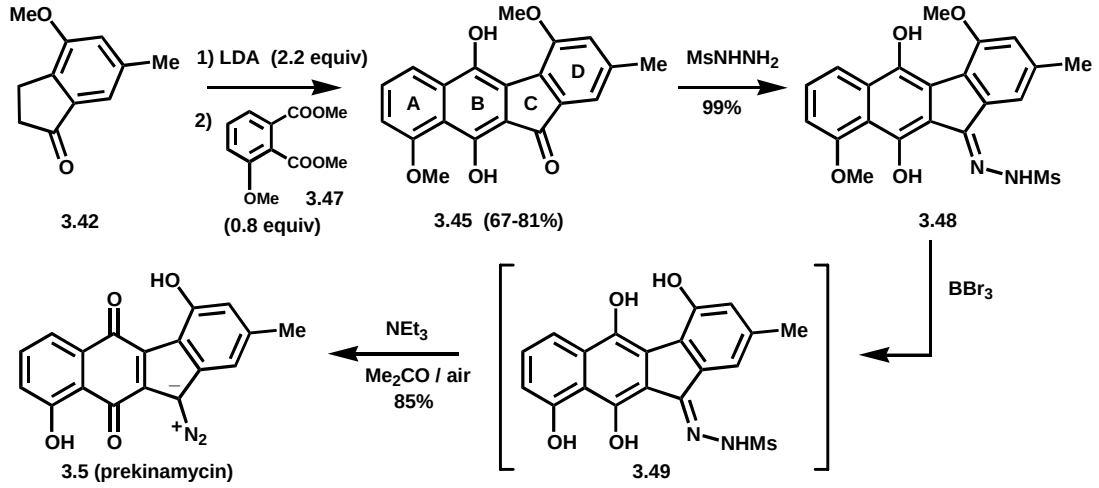
ring contained in the phthalide sulfone **3.44** with the indenone **3.43** as a precursor of the CD rings (Scheme 3.5). Demethylation of the resulting **3.45** was carried out early to avoid subsequently damaging the sensitive diazo group which was installed through hydrazone formation followed by oxidation with Fetizon's reagent. This sequence yielded prekinamycin (**3.5**) in 13.5% overall yield from commercial materials.



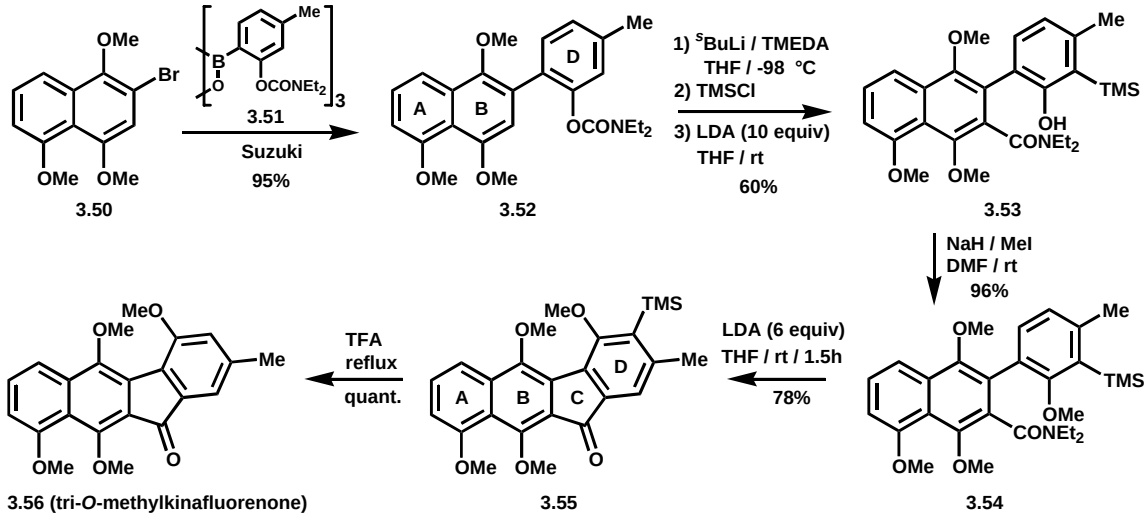
Scheme 3.5

Recently, Birman has described an even simpler approach to Hauser's intermediate **3.45** (Scheme 3.6).[30] Here, the B ring was obtained through sequential and regioselective bisacylation of the indanone **3.42** with the dimethyl phthalate **3.47**. A one-pot demethylation/oxidation of the hydrazone **3.48** provided further improvement of Hauser's synthesis and gave the target in 34-41% overall yield. Our group has also embarked in this challenge with the aim of demonstrating the advantages of combined directed metalation-cross coupling regimens in natural product synthesis (Scheme 3.7).[31] Thus, **3.52** was obtained by Suzuki cross coupling of **3.50** with the boroxine **3.51** while the DreM chemistry (see Section 1.1.6) was used to rapidly build the C ring of **3.55**.

Desilylation of **3.55** furnished, in 18% overall yield, tri-*O*-methylkinafluorenone (**3.56**), which had been previously converted into prekinamycin.[9,29]



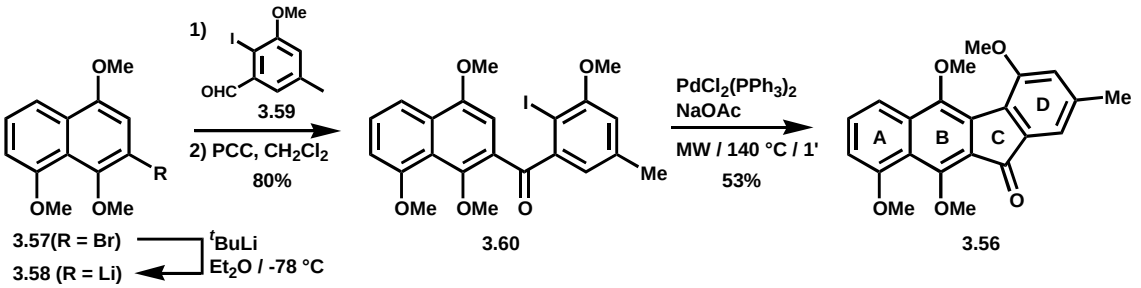
Scheme 3.6



Scheme 3.7

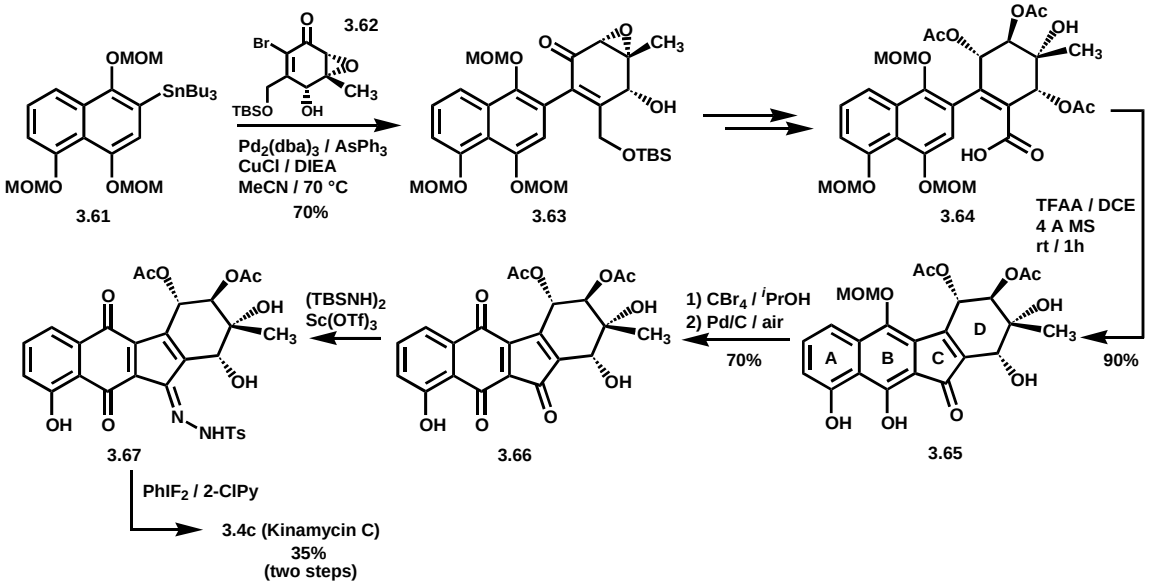
Jones's strategy towards the same target **3.56** is similar; however, the choice of an isomerically different starting oxygenated naphthyl bromide **3.57** is reflected in the inverse order of steps for the construction of the C ring (Scheme 3.8).[32] Metal-halogen

exchange of **3.57** to **3.58** and quench of the latter with benzaldehyde **3.59** bridged the AB ring system and the ring D with a carbonyl group. Then, an intramolecular Heck reaction[33] completed the formation of ring C (**3.56**).



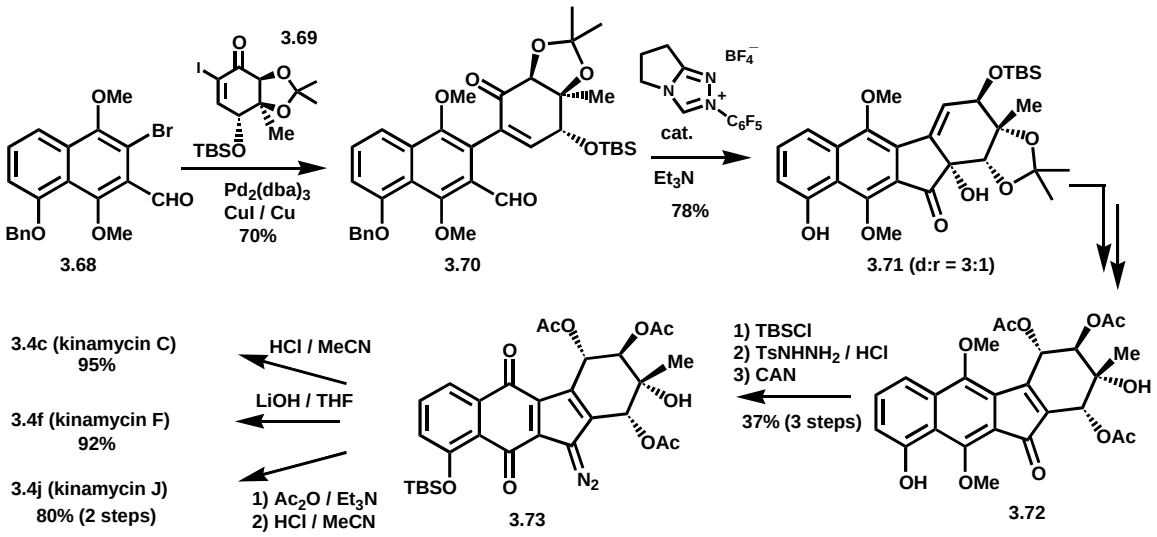
Scheme 3.8

The Porco and Nicolaou approaches to (-)-kinamycin C also rely on the cyclization of the AB/D ring system obtained through cross coupling. In Porco's strategy, fragments **3.61** and **3.62** were linked under Stille conditions to give **3.63** and, upon manipulation of the complex D ring, afforded the acrylic acid **3.64**. This was subjected to annulations by an efficient Friedel-Crafts reaction under which conditions two MOM protecting groups were also removed to yield **3.65** (Scheme 3.9).



Scheme 3.9

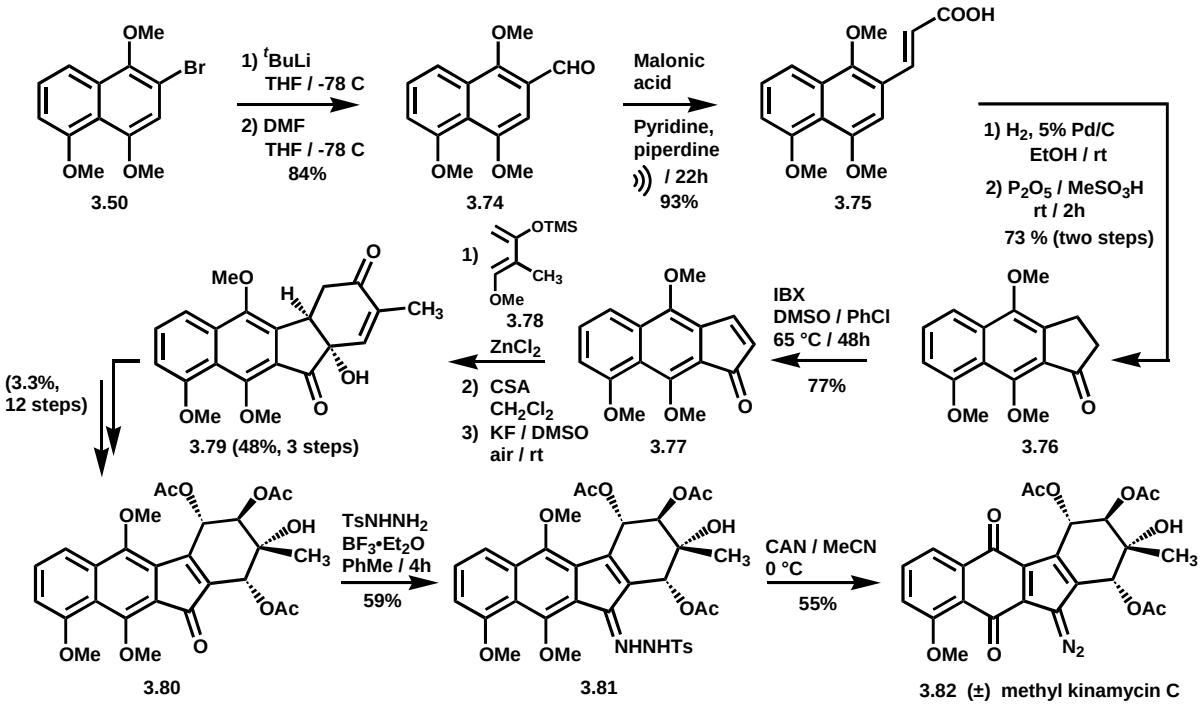
Unlike in Hauser's and Birman's syntheses of prekinamycin (Schemes 3.5 and 3.6, respectively), the oxidation of the hydroquinone B ring (**3.65** → **3.66**) was effected before the hydrazone formation (**3.67**); the remaining iodonium-mediated oxidative step yielded kinamycin C (**3.4c**) in 1.1% overall yield. Nicolaou's strategy towards the tetracyclic backbone is quite similar to that of Porco but relies on the Ullmann coupling of halides **3.68** and **3.69** followed by a benzoin condensation that gives an inconsequential 3:1 diastereomeric mixture of **3.71** in 78% yield (Scheme 3.10). As in the previous approaches, hydrazone formation and oxidation, the latter carried out with cerium ammonium nitrite, are the final steps to kinamycin C (3.1% overall yield). Full acetylation and deacetylation of kinamycin C yield kinamycin F (**3.4f**) and J (**3.4j**), respectively.



Scheme 3.10

Ishikawa's synthesis is somewhat more linear in that the starting material **3.50** (Scheme 3.11), also used by Snieckus (Scheme 3.7), was subjected to further annulation to the benzo[*f*]indenone **3.77**, which then took part in a Diels-Alder reaction with the

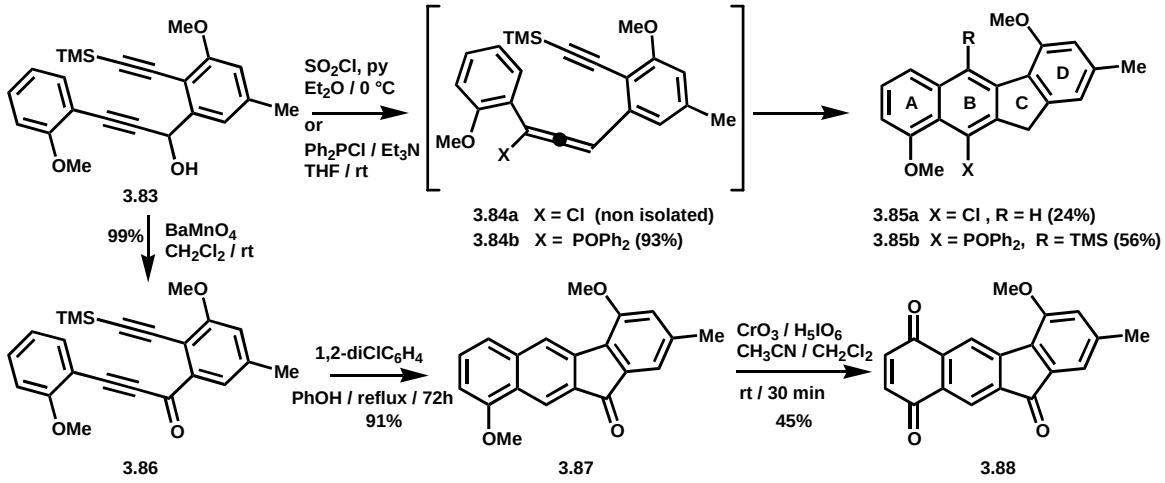
Danishefsky-type diene **3.78** to afford **3.79**. With the D ring still in the early stages of elaboration, the tetracyclic product was stepwise oxygenated and acetylated with heavy tolls in terms of yield (3.3%, 12 steps). The final steps paralleled Nicolaou's diazotization sequence (Scheme 3.10); however, unlike in the Porco and Nicolaou approaches, the choice of the 5-*O*-methylated starting bromide **3.50** as starting material limited the synthesis to methylated (±)-kinamycin C (**3.82**, Scheme 3.11).



Scheme 3.11

Lastly, Echavarren's original tactic towards prekinamycin is worthy of review, albeit problems in the oxidation of the benzo[*b*]fluorene core interrupted the synthesis only a few steps from the target (Scheme 3.12).[34] The preparation of the tetracyclic backbone relies on an arylalkyne/allene or arylalkyne/alkyne intramolecular cycloaddition. The allene moiety of **3.84a**, produced *in situ* through S_Ni' of the chlorosulfite derivative of **3.83**, is involved in a [4+2] cycloaddition with the neighbouring triple bond, providing

the 6-6-5-6 ring system of **3.85a**. Although the low yields of this process (24%) were improved by using a phosphorylated derivative of **3.83** instead of the chlorosulfite, the intended oxidation of the B ring of **3.85b** led instead to the formation of rings A and/or D oxidized products. The alternative arylalkyne/alkyne cycloaddition of **3.86** proved even more effective (91%), but all oxidative agents tested on **3.87** targeted, once again, its A ring (**3.88**).

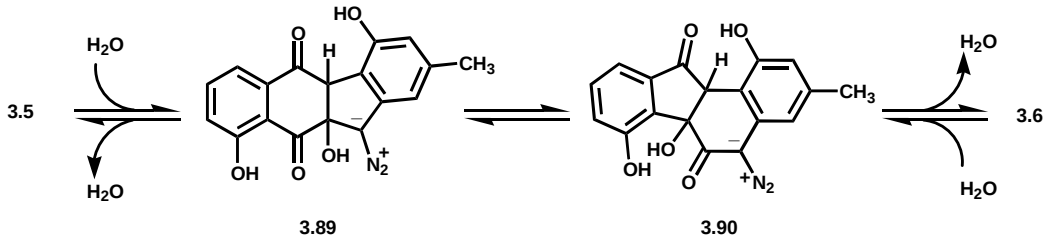


Scheme 3.12

3.1.4. Isoprekinamycin

The structural resemblance of prekinamycin and isoprekinamycin and their isolation from cultures of the same *Streptomyces* suggest a common biogenetic origin. Upon establishing the structure of CpdA, Dmitrienko fed [1,2-$^{13}C_2$]acetate to *Streptomyces murayamaensis* and isolated isoprekinamycin whose isotopic labelling pattern was consistent with the hypothesis of an interconversion between the diazobenzo[*b*]- and [*a*]fluorene systems (Scheme 3.13). Such equilibration, supported by calculations that estimate the diazobenzo[*b*]fluorene skeleton only 2.4 kcal/mol more stable than its [*a*]-

isomer, may occur through reversible hydration of **3.5** to **3.89**, followed by 1,2-carbon shift to **3.90** and dehydration.



Scheme 3.13

This hypothesis has suggested a biosynthetic relationship between benzo[*a*]fluorene-based fluostatins A-E[35] (isolated from other strains of *Streptomyces*) and kinamycins. However, considerable structural differences (both regiochemical and stereochemical) between the nominal homologues (**3.91** with **3.17**[36], **3.92** with **3.93**) must be explained before these analogies can be considered supporting evidences of this proposal (Fig. 3.6). Isoprekinamycin displays a modest antibacterial and anticancer activity towards CHO (IC_{50} = 5.8 μM) and K562 human leukemia cells (IC_{50} = 6.4 μM).[37,38]

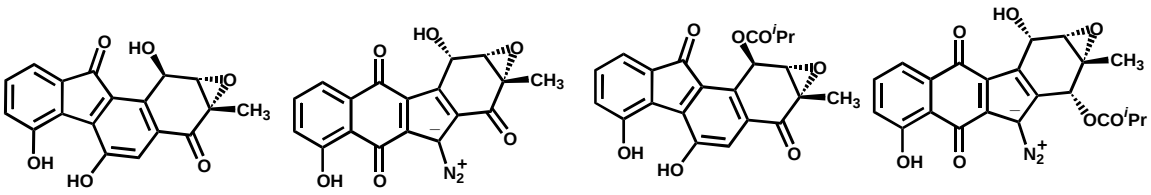
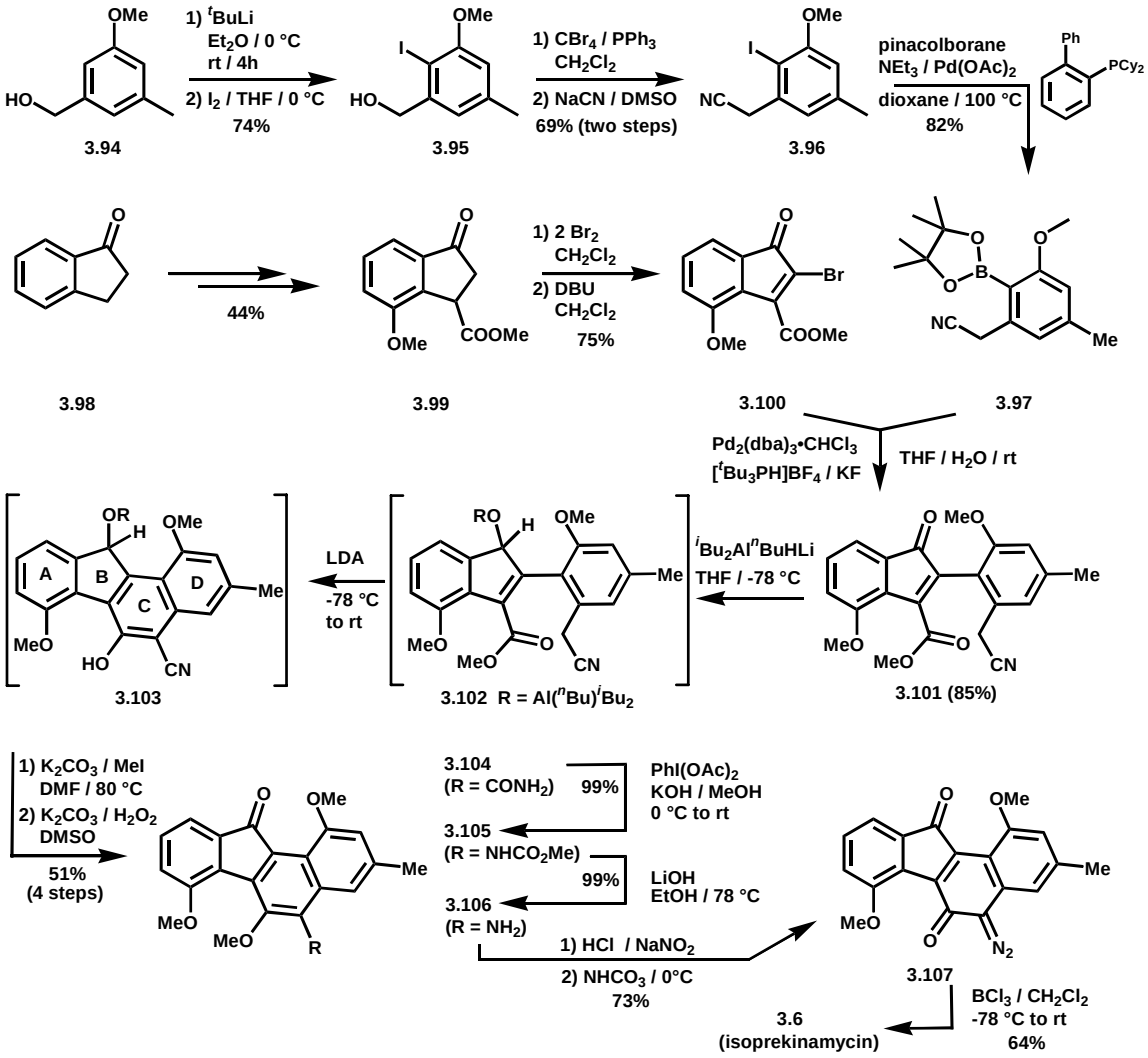


Figure 3.6 Structures of Fluostatins C and D and their Hypothetic Kinamycin Counterparts 3.17 and 3.93

Dmitrienko has recently completed the only known synthesis of isoprekinamycin or of any other benzo[*a*]fluorene natural product. As seen in several of the previous approaches to kinamycins and prekinamycin, construction of the AB/D ring system was

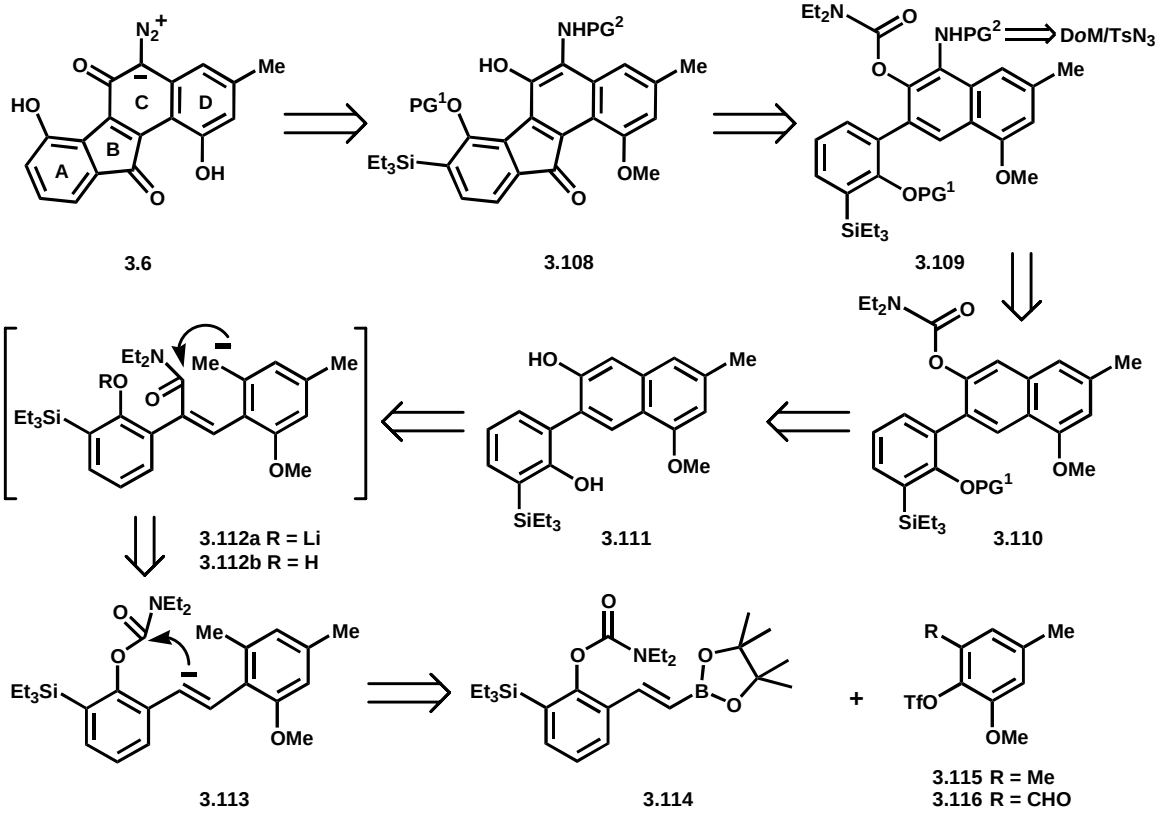
the initial focus of this strategy to **3.6** (Scheme 3.14). Thus, Suzuki coupling of **3.100** with the boropinacolate **3.97** under Fu's non-basic conditions yielded **3.101** in 85% yield. The bromide **3.100** was accessed through bromination/dehydrobromination of the known indanone **3.99**, in turn obtained from commercially available dihydrocoumarin **3.98** in 44% yield (4 steps). The boronate **3.97** was derived from 3,5-dimethylanisole, which was hydroxylated in low yield (**3.94**, 28%) and then iodinated through the D*o*M protocol in 74% yield (**3.95**). Cyanation of **3.95** to **3.96** followed by palladium-catalyzed coupling with pinacolborane furnished the coupling partner **3.97**. The formation of ring C, which relies on a Dieckmann-type reaction (**3.102** → **3.103**), was complicated by a competing intramolecular aldol reaction involving the ketone functionality. This problem was solved through reduction of **3.101** with the complex ^{n}BuLi/DIBAL to give **3.102** and *in situ* Dieckmann condensation to furnish **3.103**. The crude product was *O*-methylated and subjected to H_2O_2/K_2CO_3 oxidation which effected hydrolysis of the amide while restoring the keto functionality to give **3.104**. A modified Hoffmann rearrangement in the presence of methanol provided the carbamate **3.105** which was easily hydrolyzed (**3.106**) and diazotized (**3.107**). Curiously, demethylation with BCl_3 was performed in the last step without serious consequences on the sensitive diazo group. The synthesis includes 12 steps from commercially available 3,5-dimethylanisole and provides the target molecule in 2.3% overall yield. When superimposed to a computed structure of prekinamycin, the crystal structure of isoprekinamycin showed an excellent alignment of the oxygen and nitrogen atoms in spite of the different backbone. This observation suggests that diazobenzo[*a*]- and [*b*]fluorenes skeletons are carriers of the same pharmacophore.



Scheme 3.14

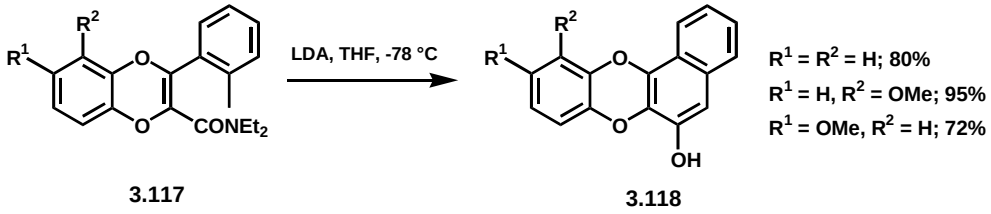
3.2. Retrosynthetic Analysis of Isoprekinamycin

In our synthetic strategy, boldly based on metalation chemistry, we envisaged the synthesis of the benzo[*a*]fluorenone skeleton of isoprekinamycin by application of the proven potential of the DreM reaction. Thus, following the *ortho*-amination of carbamate **3.110** through DoM,[39] the stepwise or tandem DreM sequence (carbamoyl migration – ring closure) already exploited by Mohri, was anticipated to furnish **3.108** (Scheme 3.15). Full deprotection of this intermediate and diazotization, as for Dmitrienko's precedent, will give the target natural product **3.6**.



Scheme 3.15

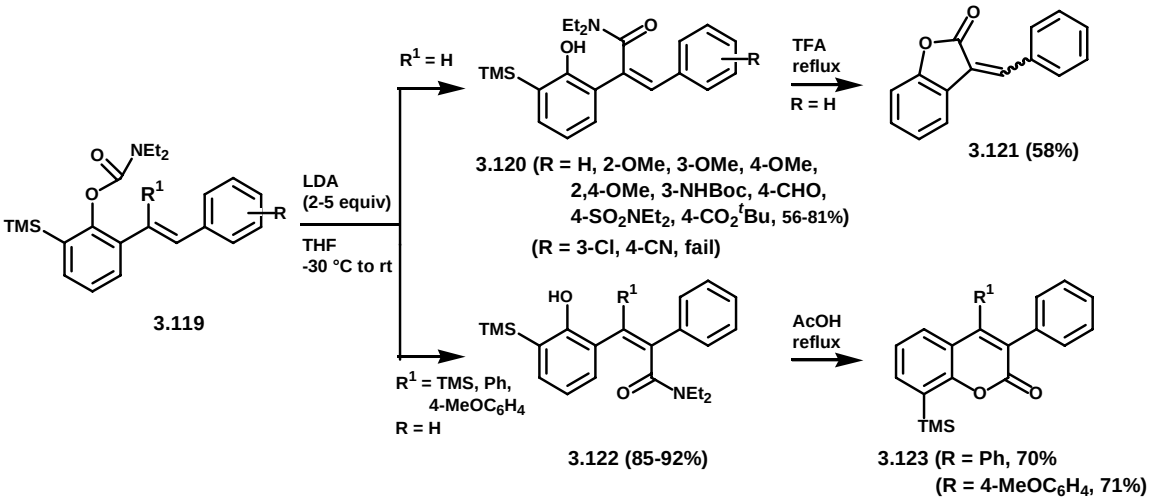
The synthesis of naphthol **3.111** was based on the anionic intramolecular cyclization of the cinnamide **3.112a** which constitutes a non-aromatic analogue of our general vinylogous DreM protocol (see Section 1.1.3) and which has been applied by Coudert for the synthesis of naphthols **3.118** as intermediates towards potential anticancer agents. (Scheme 3.16).[40]



Scheme 3.16

In our synthetic plan, the construction of the cinnamide **3.112b** was to be based on a methodology developed in our group by M.A. Reed, involving the stereoselective *O→C*

ortho vinyl carbamoyl rearrangement of 2-*O*-carbamoyl stilbenes (Scheme 3.17).[41] This work showed that, upon blocking the possible anionic Fries rearrangement by silylation of the unsubstituted *ortho* position, LDA treatment of carbamoyl stilbenes **3.119** elicits regioselective deprotonation of the α-vinyl position or, where this is substituted, deprotonation of the β-vinyl position. A rapid 1,4- or 1,5-carbamoyl translocation follows, resulting in the formation of *cis* α-phenylsubstituted cinnamides **3.120** or **3.122**, respectively. These products may be easily converted into variously substituted isoaurones **3.121** and useful coumarins **3.123** upon refluxing in acidic media.



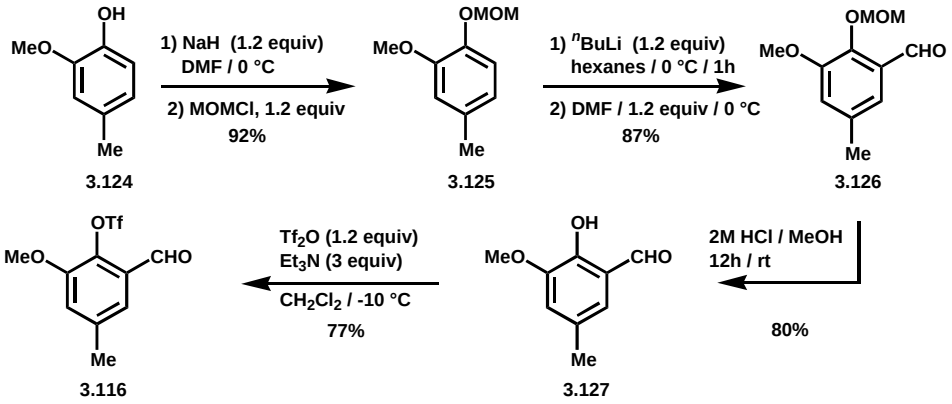
Scheme 3.17

Thus, in our case, carbamate **3.113** (Scheme 3.15), accessible by Suzuki cross coupling of the pinacol ester **3.114** with the triflate **3.115**, was chosen as a reliable source of the cinnamide **3.112b**. Interestingly, unless protection of the phenol group of **3.112b** proves beneficial for the following anionic reactions, carbamoyl translocation and ring closure (**3.113** → **3.111**) may be envisaged as a one step process.

3.3. Results and Discussion

3.3.1. Synthesis of Coupling Partners 3.114 and 3.116

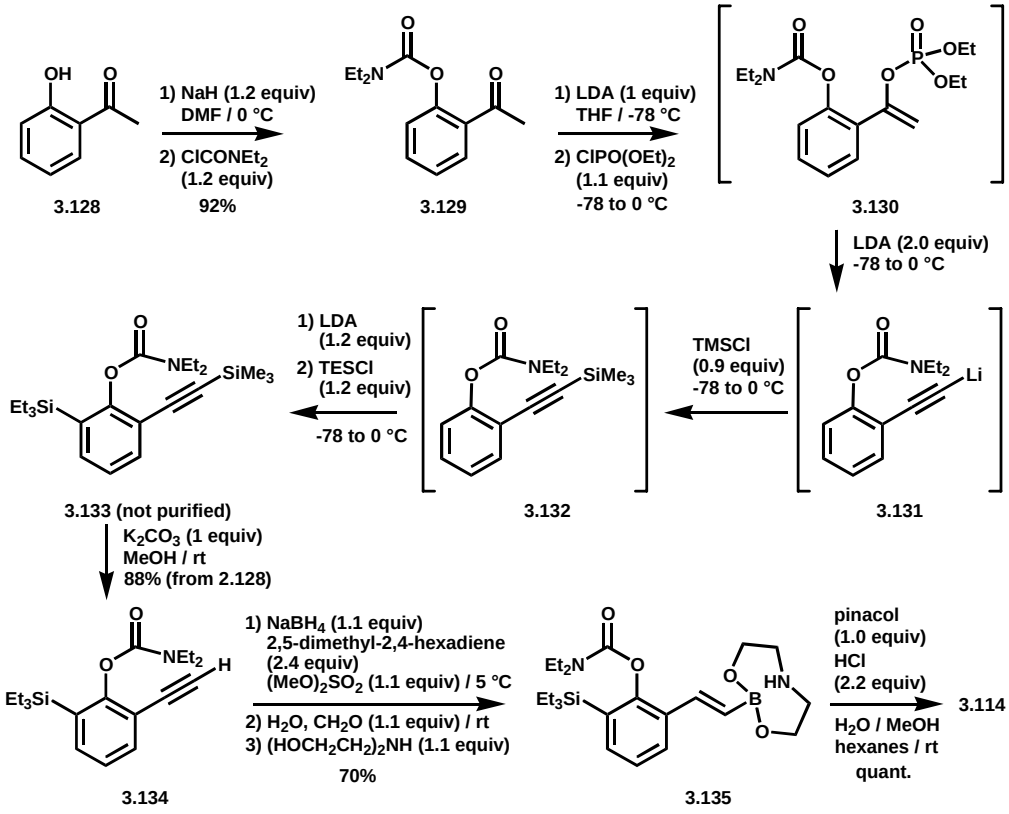
From previous experience in the Pd-catalyzed Suzuki coupling of crowded partners, we had learned that the presence of a formyl group adjacent to the coupling site generally increases the efficiency of the reaction.[42] Thus, rather than suffering the hindrance effect of the methyl group in the coupling of **3.115** (Scheme 3.15), we chose to couple the benzaldehyde **3.116** with **3.114** and modify the formyl group of the coupling product **3.136** (Scheme 3.21). The synthesis of the triflate **3.116** was carried out from the commercially available **3.124** and involved the installation of a removable DMG, functional to the anionic *ortho*-formylation of the ring (Scheme 3.18). Thus, D*o*M of the MOM-derived cresol **3.125** using ^{n}BuLi/TMEDA followed by DMF quench afforded the benzaldehyde **3.126** in 87% yield. Sequential deprotection and triflation of the latter provided the coupling partner **3.116** in 49% overall yield (4 steps).



Scheme 3.18

The styryl borolane **3.114** was constructed starting from the carbamate **3.129**, which was readily obtained from commercially available 2'-hydroxyacetophenone (Scheme 3.19). The conversion of the keto group of **3.129** to the alkyne moiety of **3.133** was carried out in a one-pot sequence of reactions which include the *o*-silylation of the ring. Thus, using an interesting Negishi protocol,[43] the lithium enolate of **3.129** was trapped as the

diethylphosphate **3.130** which, upon addition of more LDA, underwent elimination to give the lithium acetylide **3.131**. Following protection of this acetylide as its TMS derivative, a D*o*M-silylation sequence was now integrated in this multistep reaction to provide **3.133** as the ultimate product. The differential bis-silylation of the latter was suggested by the high cost of Et_3SiCl, an obligatory choice for the protection of the *ortho* position in view of the tendency of the Me_3Si group to undergo deprotonation and thus lead to an unwanted migration of the carbamoyl group.[31,41]



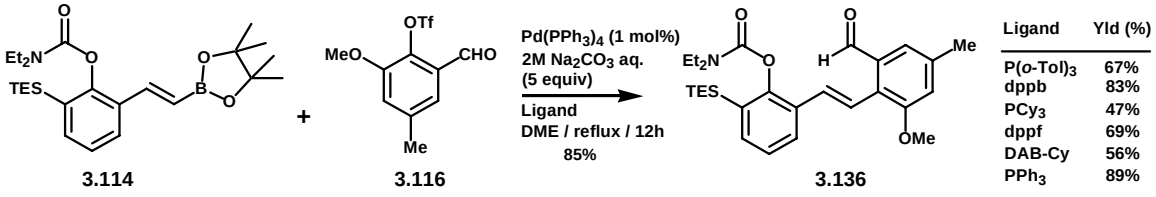
Scheme 3.19

The desilylation of crude **3.133** with 1 equivalent of TBAF was not selective, although some improvement was obtained with lower amounts of TBAF (0.8 equiv / rt / 30 min), provided the THF solvent contained 10% of methanol. Further optimization led to the

high yielding monodesilylation of **3.133** (88% from **3.129**) under milder conditions (methanol / rt / 30 min) using inexpensive K_2CO_3. The hydroboration of the acetylene **3.134** was carried out applying the protocol developed by Kalinin which uses di(isopropylprenyl)borane, a novel reagent that, while maintaining a high anti-Markovnikov regioselectivity, produces boranes which are readily hydrolizable to boronic acids without the need of strong oxidizing agents.[44] Di(isopropylprenyl)borane was generated *in situ* from 2,5-dimethyl-2,4-hexadiene and borane, in turn obtained from $NaBH_4$ and dimethyl sulfate. For purification purposes, the boronic acid was isolated as the crystalline diethanolamine ester **3.135** and then quantitatively converted into the pinacol boronate **3.114**.

3.3.2. Synthesis of the Key Naphthol Derivative 3.111

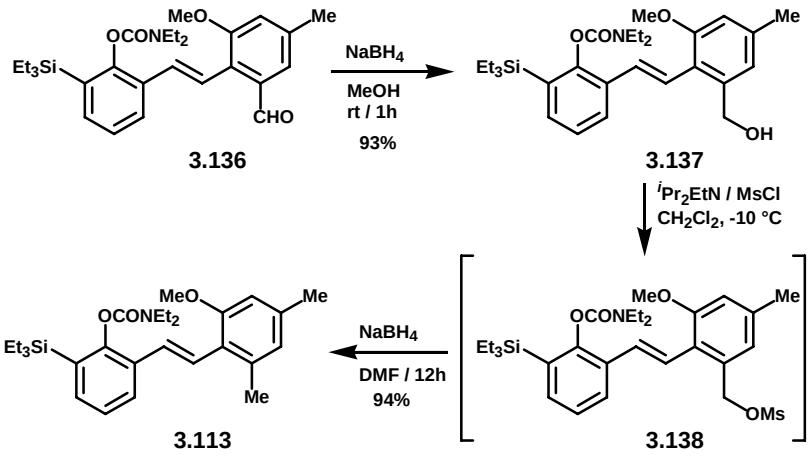
With the coupling partners in hand, a few ligands were screened for the Pd-catalyzed Suzuki coupling reaction (Scheme 3.20). Under aqueous conditions, dppb and PPh_3 gave the best results, and the reaction was scaled up using $Pd(PPh_3)_4$ which, with 1% catalyst loading, furnished the stilbene **3.136** in 85% yield.



Scheme 3.20

The deoxygenation of **3.136** was carried out through an efficient three step protocol that begins with the $NaBH_4$ reduction of the formyl group to give the benzyl alcohol **3.137** (Scheme 3.21). Tosylation of **3.137** gave only traces of the product even in the presence of DMAP and after reflux conditions, while mesylation was immediate and complete at

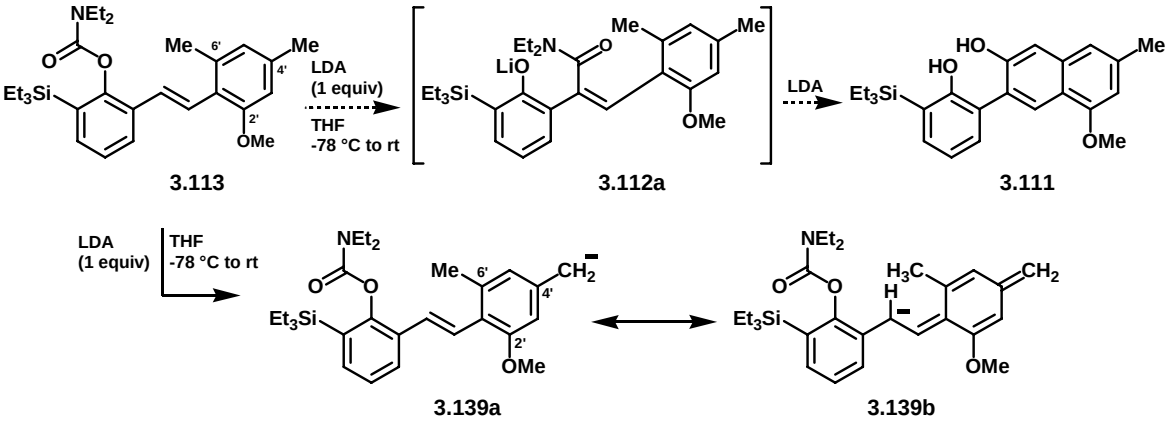
−10 °C. The crude mesylate **3.138**, upon a second reduction using $NaBH_4$, furnished analytically pure stilbene **3.113** in 94% yield.



Scheme 3.21

Compound **3.113** was now expected to undergo the anionic rearrangement, the lynchpin of the proposed synthetic strategy (Scheme 3.15). Since most DreM reactions and Reed's carbamoyl translocation proceed with some excess of LDA, this base was tested first. The visible progress of the reaction deserves comments. Upon addition of the first drop of LDA to **3.113** at −78 °C, the THF solution became dark blue although TLC revealed only the presence of starting material. Addition of one full equivalent of base did not affect the reaction progress until the temperature was allowed to slowly rise to −10 °C. At this point, the colour gradually changed to dark pink and the starting material underwent decomposition (TLC analysis), leading to a non UV-active foamy material whose NMR analysis was utterly uninterpretable. It was hypothesized that the presence of the additional $C_{4'}$-methyl in **3.113** promotes deprotonation to give the anion **3.139,** unlikely to trigger the carbamoyl migration due to the extensive charge delocalization (Scheme 3.22). Particularly, the quinoid resonance structure **3.139b** may explain the

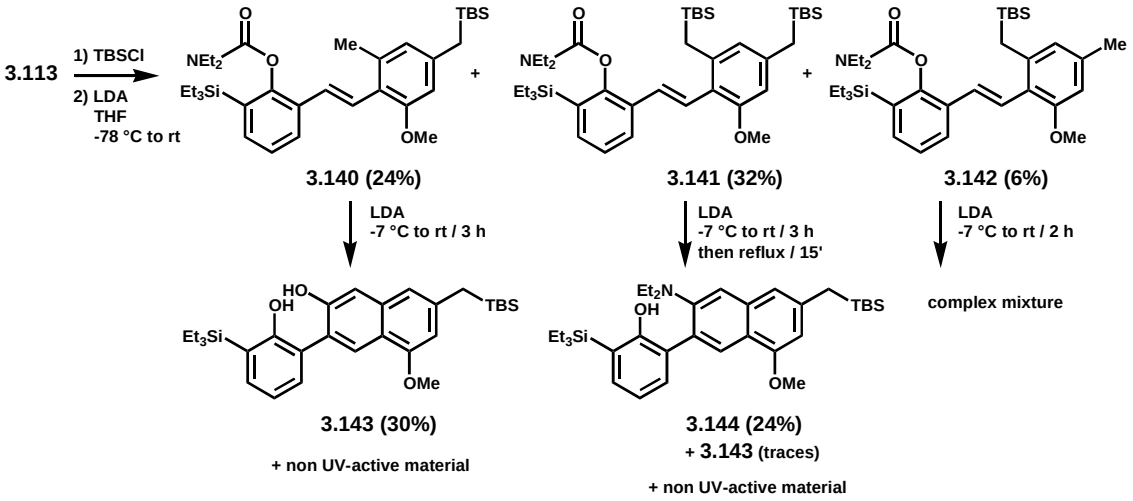
appearance of the deep blue colour and shows the unlikelihood of a second deprotonation at the α-vinyl position.



Scheme 3.22

Based on this interpretation, it was hypothesized that any factor minimizing the contribution of **3.139b** and favouring the α-vinyl deprotonation may at least allow the first step of the LDA-induced cascade reaction **3.113** → **3.112a**. Silicon has the ability to stabilize α-carbanions through the overlap of the α-carbon-metal bond with a silicon *d* orbital and/or with a σ* orbital of an adjacent silicon-carbon bond.[45] Through this stabilization, a silicon atom directly attached to the $C_{4'}$-methyl group of **3.113** was expected to harness the negative impact of the tolyl anion on this reaction and perhaps divert electron density away from the double bond, thus normalizing the acidity of the α-vinyl position. Thus, silylation of **3.113** was attempted in the hope that the trapping of the *in situ* base-compatible silicon electrophile would prevent decomposition (Scheme 3.23). More than 1 equivalent of *in situ* TBSCl was found to be necessary in order to prevent decomposition and, independently of the base used (LiTMP, LDA (use of LiHMDS resulted only in recovery of starting material), selective silylation could not be

achieved. **3.113** slowly began to undergo reaction at –10 °C, invariably generating mixtures of the monosilylated isomers **3.140** and **3.142** along with the doubly silylated product **3.141**. Use of large excess of LDA/TBSCl (5 equiv each) gave **3.141** as the main product (88%) together with traces of the monosilylated isomers. A delicate chromatographic separation gave pure samples of all three products and the two monosilylated isomers, **3.140** and **3.142,** were structurally elucidated and differentiated through HMBC NMR experiments. Upon treatment with excess of LDA at –7 °C, the THF solutions of the separate silylated stilbenes **3.140** and **3.142** once again turned blue and remained unchanged until they were stirred at rt for a few hours. Under these conditions, however, **3.140** led to the formation of the expected naphthol **3.143**, although in low yields (30%), demonstrating that the predicted tandem DreM reaction is indeed feasible.



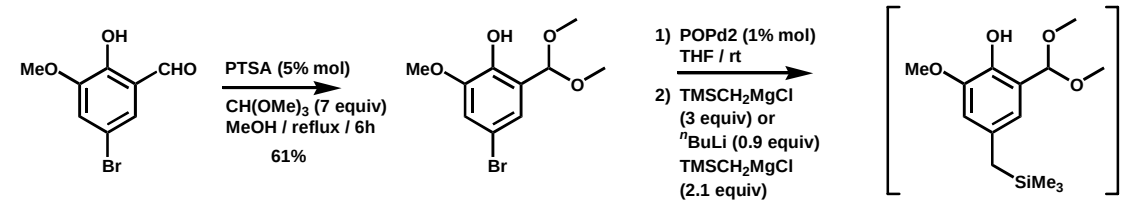
Scheme 3.23

On the other hand, the disilylated derivative **3.141**, although shown to undergo slow reaction at rt, yielded, after brief refluxing in THF, traces of **3.143** but mainly the 2-naphthylamine **3.144** (24%) through a Peterson elimination reaction. Finally, **3.142** decomposed on contact with LDA, although at a slower rate than **3.113**. Despite the poor

yield, the isolation of naphthol **3.143** was welcomed with delight and great confidence that optimization of this reaction would provide sizeable amounts of this key intermediate. Although this optimism was not realized on gram scale for the preparation of any of the monosilylated products, a desilylation test on **3.141** using TBAF at rt showed that the methyl groups could be easily reconstituted to give **3.113** (see Experimental Section).

3.3.3. Large Scale Preparation of Silylated Carbamoyl Stilbene 3.152

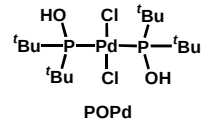
The continuation of the proposed strategy to isoprekinamycin required a scalable and reliable route for the provision of sufficient TBS derivative **3.140** for further optimization of the DreM process to **3.143.** This required retracing the entire route to a new partner, the silylated derivative of triflate **3.116** which, in Suzuki coupling with **3.114** (Scheme 3.25), appeared to be the most feasible route to obtain useful amounts of the stilbene **3.140**. To this end, the known bromide **3.145**[46] was cross coupled with $TMSCH_2B(OH)_2$ to give the benzylsilane **3.148** (Scheme 3.24). However, difficulties encountered in the isolation of $TMSCH_2B(OH)_2$ and $TMSCH_2BF_3K$[47] and the commercial availability of $TMSCH_2MgCl$ (but not of $TBSCH_2MgCl$), diverted the attention to the alternative, albeit less straightforward, Kumada coupling of $TMSCH_2MgCl$ with **3.145**, despite the protection requirements for the latter compound. Testing of a number of Pd and Ni catalysts on the coupling of the TMS ether of **3.146** with $TMSCH_2MgCl$ showed that most Ni catalysts (entries 1-7) were effective, but debromination was often a significant side reaction (Scheme 3.24).



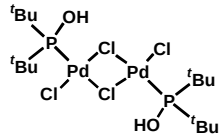
3.145 3.146 3.147

Cross coupling of the TMS ether of 3.146 with $TMSCH_2MgCl$ (1.5 equiv)

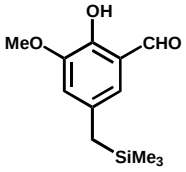
Entry	Catalyst*	Yld (GC)	Entry	Cat. / Ligand*	Yld (GC)
1	$NiCl_2$dppf	50%	8	$Pd_2(dba)_3$/ (1%mol) IPr•HCl (4% mol) dioxane / THF	56%
2	$NiBr_2$dppe	38%			
3	$NiCl_2P(PPh_3)_2$	74%	9	POPd (1% mol)	40%
4	$Ni(acac)_2$	32%	10	POPd1 (1% mol)	45%
5	$Ni(COD)_2$	5%	11	POPd2 (1% mol)	87%
6	CpNiCl(PPh_3)	47%	12	POPd2 (1% mol) RMgBr (2 equiv)	quant
7	CpNiCl(IMes) (1% mol)	0%			



POPd



POPd2



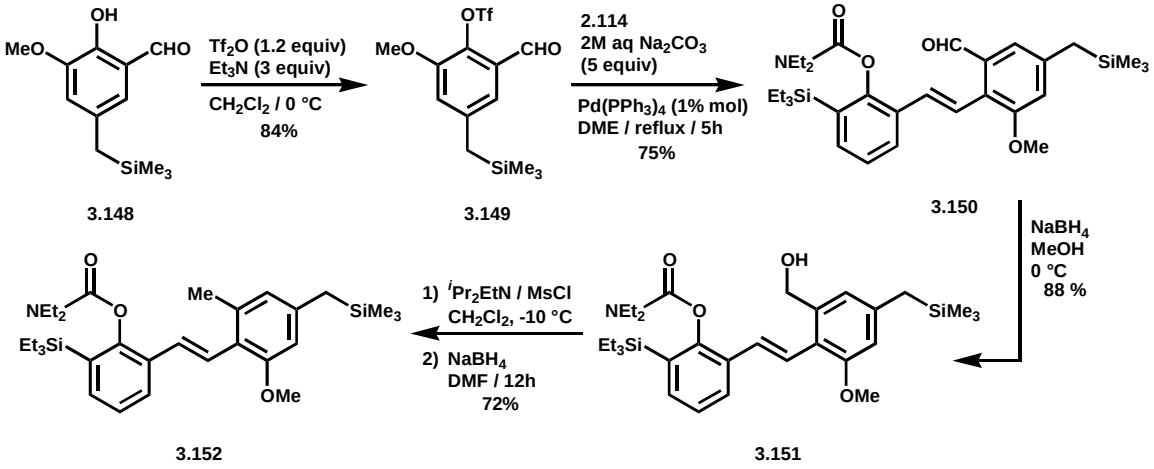
3.148

*5 mol % in THF at rt unless otherwise indicated

Scheme 3.24

The cross coupling reaction catalyzed by palladium CombiPhos catalysts[48] (entries 9-11) did not suffer this drawback and POPd2 (1% mol) was singled out for its excellent performance when 2 equivalents of the Grignard reagent were used (entry 12). The catalyst was found to be very effective on the unprotected phenol **3.146**, provided that an extra equivalent of $TMSCH_2MgCl$ was sacrificed to neutralize the phenolic hydrogen. To reduce the amount of the expensive Grignard reagent needed in the large scale preparation of **3.148**, the substrate was deprotonated with 0.9 equivalents of ^{n}BuLi before the addition of the coupling partner with the result that **3.148** was still obtained in quantitative yield. While standard deprotection of **3.147** (5% PTSA) led to partial decomposition, treatment of the crude coupling product with silica wetted with 10% aqueous oxalic acid furnished **3.148** (96%, over two steps). The vanillin derivative **3.148** was triflated (84% yield, Scheme 3.25) under the same conditions applied to its non silylated homologue **3.127** (Scheme 3.18) and the new partner **3.149** was subjected to

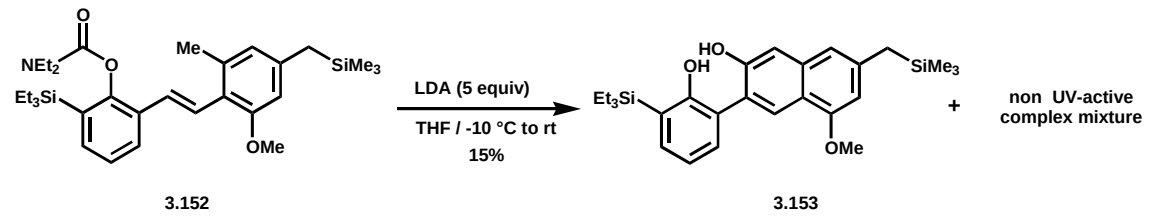
coupling under the standard aqueous Suzuki conditions with the same pinacol boronate **3.114** to afford **3.150** in an acceptable 75% yield. Under the same conditions adopted in the preparation of **3.113** (Scheme 3.21), the subsequent deoxygenation of **3.150** furnished, via intermediate **3.151,** the silylated carbamoyl stilbene **3.152** in 63% yield over two steps. The synthesis of **3.152** from **3.145** was thus achieved in 6 steps and 23% overall yield.



Scheme 3.25

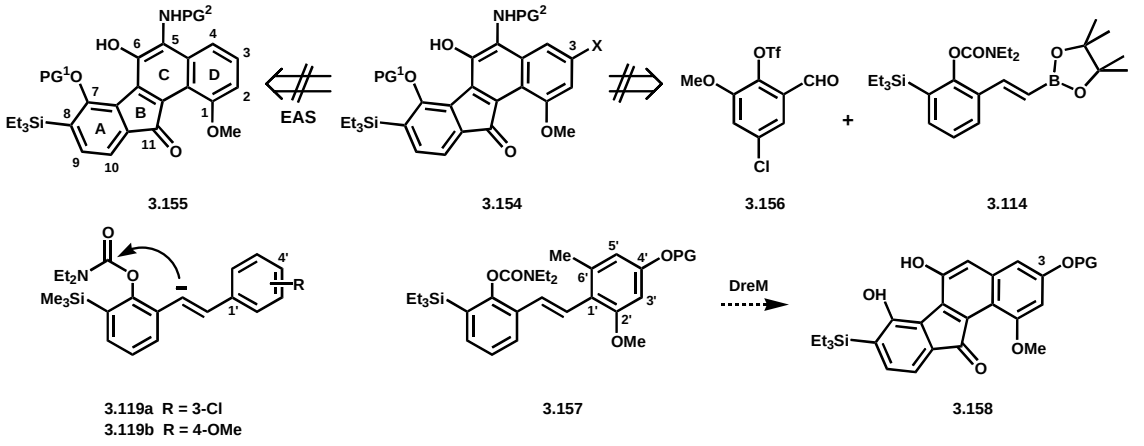
3.3.4. Unexpected Anionic Reactivity of Methylated Carbamoyl Stilbenes

The reactivity of **3.152** paralleled that of the TBS analogue **3.140**, with the same blue colour developed upon addition of the base, the same non UV-active foam as the end product and the formation of only 15% of the desired naphthol **3.153** (Scheme 3.26). Tests of the same reaction in Et_2O and hexanes, complicated by the lower solubility of LDA or LiTMP in these solvents, resulted in similar results.



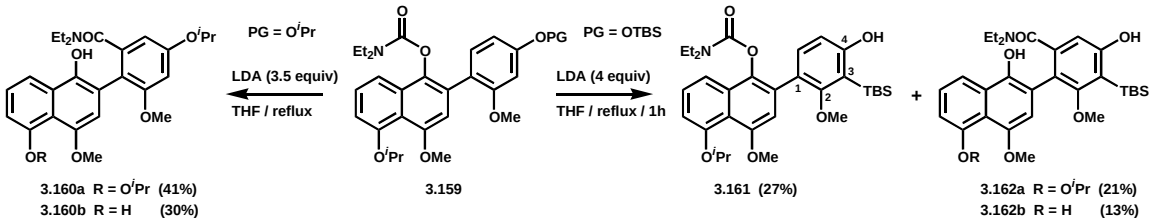
Scheme 3.26

Having faced the limited effects of the silyl group on the improvement of this reaction, a cross coupling reaction to introduce the presumably treacherous $C_{4'}$-methyl group upon conclusion of all anionic chemistry was carefully pondered as a drastic alternative. This option required the provision of a coupling leaving group capable of surviving the strongly anionic conditions leading to **3.154** because the late functionalization of **3.155** at that critical position (C_3) is not viable through EAS (Scheme 3.27). As demonstrated by Reed, attempts at the low-temperature carbamoyl translocation of a chlorine-substituted stilbene **3.119a** suffered total decomposition of the starting material, possibly due to the formation of benzyne intermediates. Thus, even a *p*-chlorinated triflate **3.156** which, unlike its bromo and iodo-analogues, may still be expected to selectively undergo coupling with **3.114** at the hindered position, was not deemed a good precursor of **3.154** (X = Cl). In contrast, the *para*-MeO substituted carbamoyl stilbene **3.119b** has been shown to undergo carbamoyl migration in 73% yield, suggesting that **3.157** should undergo smooth DreM reactions to form **3.158**. The cross coupling of alkyl/vinyl groups following a DreM reaction has been applied by James to the synthesis of defucogilvocarcins V, M and E.[49] His testing of selected protecting groups in the DreM of **3.159** highlighted the lability of the OTBS group which underwent 1,3 *O→C* migration following competing deprotonation at the 3′ position (**3.161** and **3.162**, Scheme 3.28).



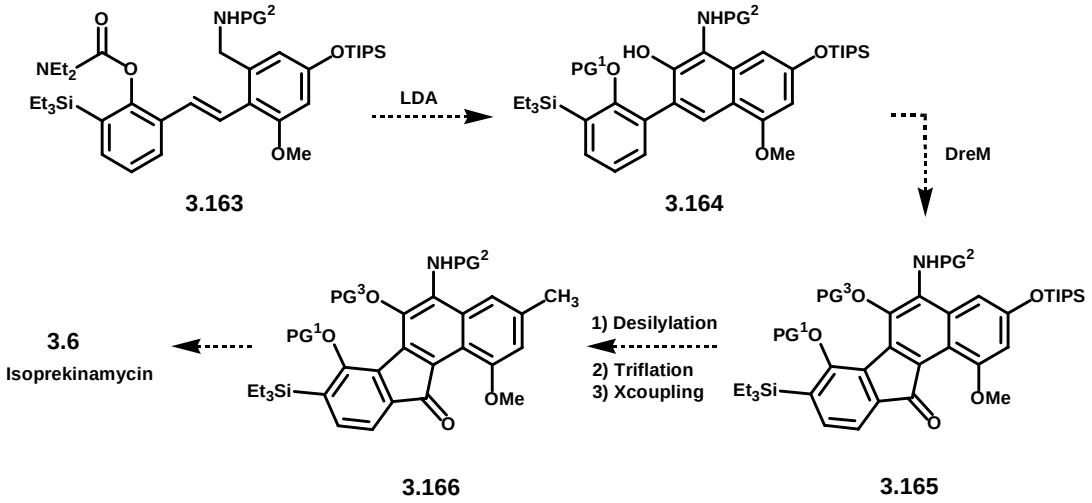
Scheme 3.27

On the contrary, replacement of the TBS protection with the robust O^{i}Pr group, as suggested by Wang's final step in the synthesis of dengibsin,[50] proved the general suitability of this choice (**3.159** → **3.160**).



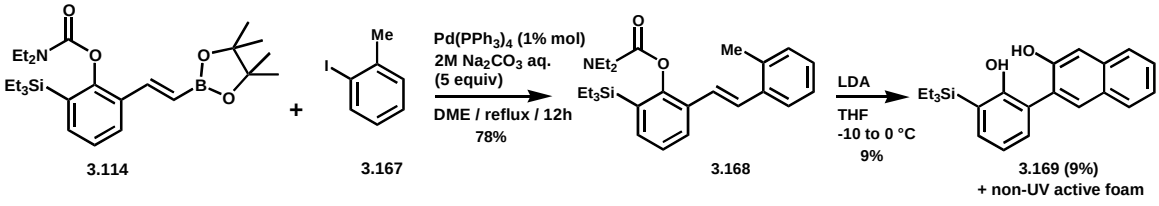
Scheme 3.28

Thus, upon conversion of the isopropoxy group of **3.158** (PG = O^{i}Pr) into a triflate group, the troublesome methyl group was considered to be easily installed. In fact, this type of strategy is currently being explored in our group by Thanh-Giau Nguyen[51] to obtain amino naphthol **3.164** from compound **3.163**, in which the amino group has been introduced at an earlier stage (Scheme 3.29). The penultimate reactions to isoprekinamycin (**3.6**) are proposed to proceed via intermediates **3.165** and **3.166**.



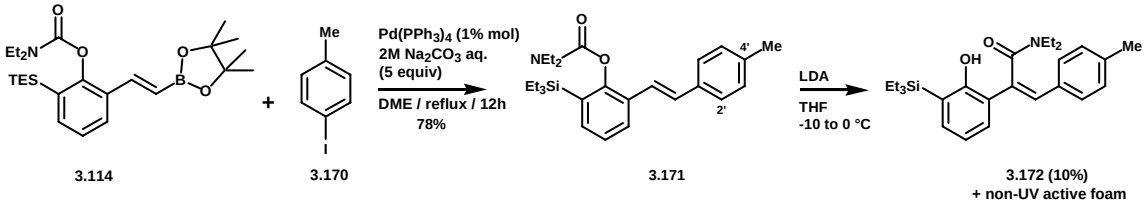
Scheme 3.29

However, an important question to be addressed was the extent that the $C_{4'}$-methyl in **3.113** contributes to the decomposition process (Scheme 3.22). For this purpose, a model stilbene **3.168** was prepared (78% yield) by cross coupling the boronate **3.114** and *o*-iodotoluene (Scheme 3.30). Upon addition of LDA at –10 °C, the THF solution of **3.168** became yellow (a resonance structure analogous to **3.139b** (Scheme 3.22) is now impossible), without, however, undergoing any chemical change. The reaction was observed to begin when the temperature reached ~ 20 °C and, after 2 hours, the starting material appeared completely consumed (TLC analysis). Chromatography of the crude mixture provided a most alarming result in that it yielded only 9% of naphthol **3.169** along with the usual non-UV active foamy material.



Scheme 3.30

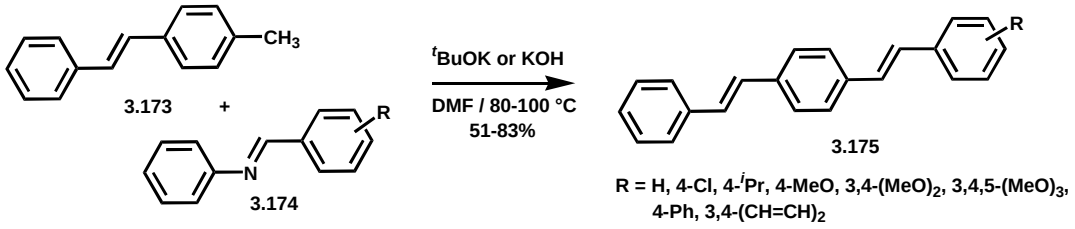
The importance of this result cannot be overstated because it demonstrates that the LDA-triggered carbamoyl translocation **3.119** → **3.120** (Scheme 3.17), observed by Reed, is not compatible with the presence of a $C_{6'}$-methyl, a critical feature in our approach to naphthols. Interestingly, a $C_{4'}$-methyl was also found to be detrimental to the reaction in question as demonstrated by an analogous test reaction with **3.171** (Scheme 3.31). The latter, obtained in 78% yield from cross coupling of **3.114** and *p*-iodotoluene, upon contact with LDA, developed the known blue colour and, once again, yielded only 10% of the migrated product **3.172**, the rest being non UV-active foam.



Scheme 3.31

The result of this experiment, in which the carbamoyl translocation of **3.171** cannot cascade into an anionic cyclization in the absence of a $C_{2'}$-methyl group, suggests that the failure of converting $C_{2'}$-methylated carbamoyl stilbenes into naphthols is not to be ascribed to a problem in the anionic annulation of the cinnamide intermediate, but to a reaction which effectively competes with the carbamoyl migration step. The similar yields in which **3.172** and **3.169** were obtained even suggest that the second step of the cascade reactions to the naphthols **3.143**, **3.153** and **3.169** (Schemes 3.23, 3.26 and 3.30 respectively) may occur in very high yield on the small amount of the cinnamide intermediates (as proven in a later experiment, see Scheme 3.54). Although, to the best of our knowledge, the benzylic LDA-deprotonation of stilbenes has not been reported, the Siegrist anionic condensation of an aryl imine (*e.g.*, **3.174**, Scheme 3.32) with methylated

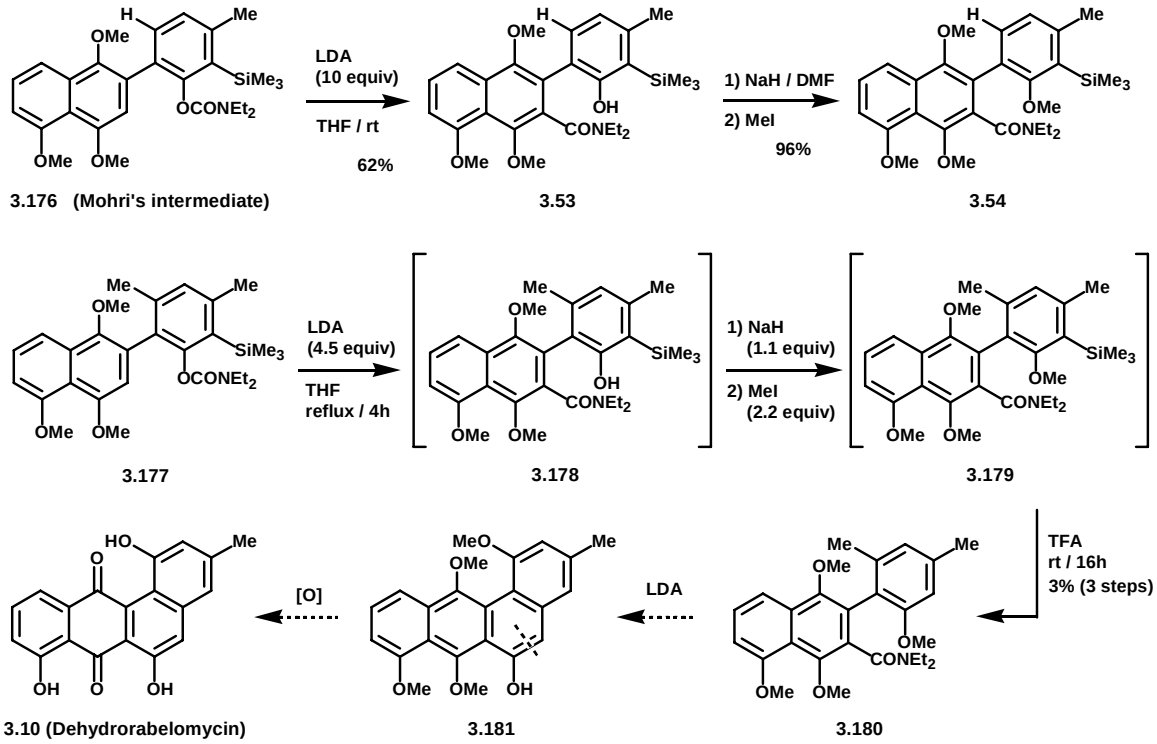
stilbene **3.173** has been advantageously applied to prepare oligomeric stilbenes useful in material science chemistry (Scheme 3.32).[52] The reaction generally occurs in the presence of ^{t}BuOK or KOH and, despite the vigorous conditions required (80-100 °C in DMF), gives generally good yields (60-90%).



Scheme 3.32

The deleterious effect of methyl groups in a DreM reaction has been experienced before by C. Kendall during the synthesis of dehydrorabelomycin (**3.10**, Scheme 3.1). Not surprisingly, since the latter is a biogenetic precursor of the kinamycins, Kendall attempted the synthesis of the fused phenanthrol **3.181**[53] (Scheme 3.33) from phenyl-*O*-carbamate **3.177** bearing a substitution pattern very similar to that of **3.176**, used by Mohri and Stefinovic in the synthesis of tri-*O*-methylkinafluorenone. Kendall's strategy was based on the migration of the carbamoyl group to the alternate ring (**3.178**), followed by a benzylic deprotonation and condensation to a 6-membered ring (**3.181**). According to his report, the initial migration (**3.177** → **3.178**) did occur, as suggested by TLC and GC-MS analysis of the crude product; however, the instability of **3.178** and of its derivatives **3.179** and **3.180** on contact with silica gel prevented their isolation in synthetically useful amounts. Only trace amounts (3%, 3 steps) of **3.180** were obtained after the crude product mixture was subjected to methylation and desilylation. Kendall suggested that **3.53** and **3.178** are remarkably different in that the latter is conformationally restricted around the Ar-Ar bond and linked the observed instability of

3.178 to its silyl group, whose removal from the crude intermediate was hypothesized as one possible step that may benefit the stability of the product.[54]

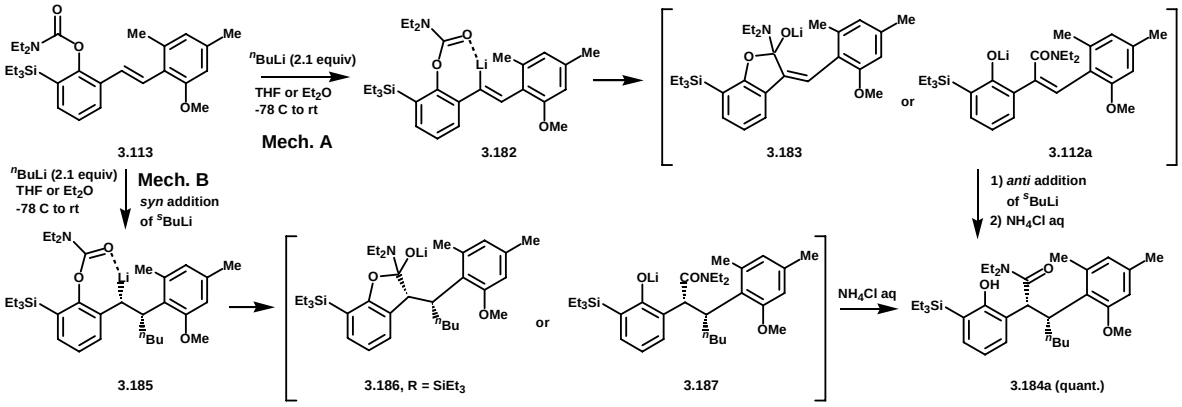


Scheme 3.33

On the other hand, **3.53** and **3.54**, Mohri and Stefinovic's close analogues of **3.178** and **3.179**, respectively, were found to be stable to silica gel chromatography under normal conditions. Thus, another interpretation of these evidences is that TLC and GC-MS analyses of crude **3.178** may have failed to detect the extensive decomposition of **3.177** on contact with LDA. Indeed, the decomposition products of most methylated stilbenes subjected to LDA during these studies towards the synthesis of isoprekinamycin were UV-inactive and non detectable by GC-MS. Following this conjecture, the DreM of **3.177** may have failed due to the presence of the additional methyl group. On the basis of the significant, albeit negative results obtained so far it became clear that progress in

this work was more likely to come from a strategy involving the selective deprotonation at the α-vinyl position of **3.113** (Scheme 3.15).

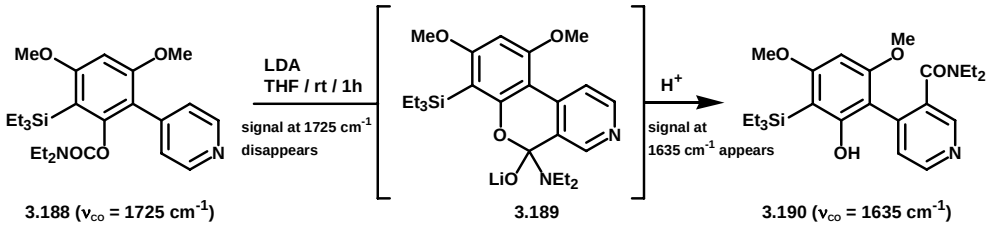
Despite the fact that virtually all DreM reactions occur under thermodynamic conditions[55] (*i.e.*, using LDA or other hindered lithium amides), ^{n}BuLi was tested, with little at stake, in the carbamoyl translocation reaction of **3.113** and, to our surprise, no decomposition or nucleophilic attack at the carbamoyl group was observed and product **3.184a** was isolated in quantitative yield (Scheme 3.34).



Scheme 3.34

Two mechanisms may be suggested for this reaction: upon α-vinyl deprotonation of **3.113**, the subsequent carbamoyl translocation gives cinnamamide intermediate **3.112a** which undergoes stereoselective Michael addition to afford the dihydrostilbene **3.184a** (mechanism A); alternatively, in a process akin to the known regiospecific carbolithiation of unsymmetrical alkenes,[56] ^{n}BuLi nucleophilically attacks the β-vinyl position of **3.113** and the anion generated (**3.185**) is quenched intramolecularly through the translocation of the neighbouring carbamoyl group (**3.185** → **3.187**, mechanism B). During studies towards the total synthesis of schumanniophytine, T. Macklin monitored the DreM reaction of **3.188** by React-IR (Scheme 3.35).[57] While the signal at 1725 cm^{-1}

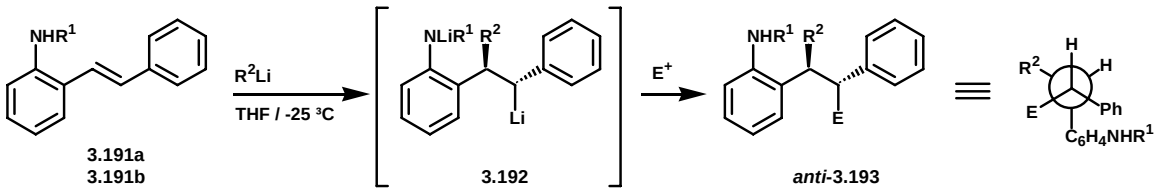
(corresponding to the SM) gradually disappeared upon its addition to LDA, the band at 1635 cm^{-1} (due to the product **3.190**) appeared only upon quench of the reaction mixture with a proton source. This experiment suggests that the carbinolamine oxide intermediate **3.189** is stable under LDA conditions and may therefore be trapped prior to ring opening to the aryl nicotinamide **3.190**.



Scheme 3.35

Following this evidence, a more precise description of the formation of **3.184a** may invoke the intermediacy of the species **3.183** (Mechanism A) and **3.186** (Mechanism B, Scheme 3.34). The carbolithiation of unsymmetrical stilbenes has been demonstrated by O'Shea with compound **3.191a** containing, as in the case of **3.113**, a DMG (*N*-Boc group)[58] and the analogue **3.191b** containing the *N*-benzyl group, whose DMG ability remains unknown (Table 3.1). In both cases, however, all isomeric butyllithiums added with complete α-regiochemistry to the α-vinyl position of **3.191a,b**. The opposite regioselectivity (nucleophilic attack at the β-vinyl position) observed in the formation of **3.184a** (Scheme 3.34), has precedent in the carbolithiation of *o*-aminostyrenes **3.194**[59] and *trans* β-methylstyrenes **3.197** which gave, upon quench with selected electrophiles, 3-substituted indoles **3.196** and **3.199** (Scheme 3.36).[60]

Table 3.1 Carbolithiation of α-Amino-(*E*)-Stilbenes with Alkyllithiums

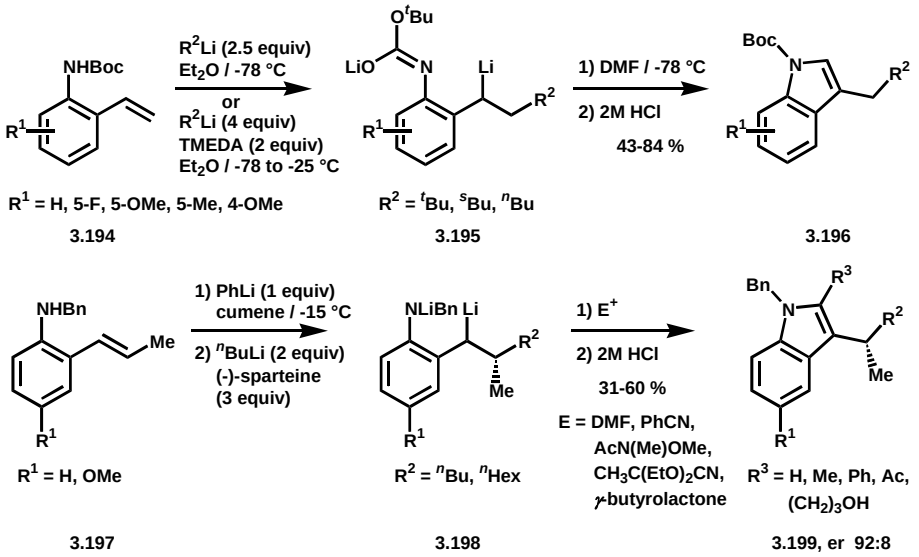


3.191a
3.191b

3.192

anti-3.193

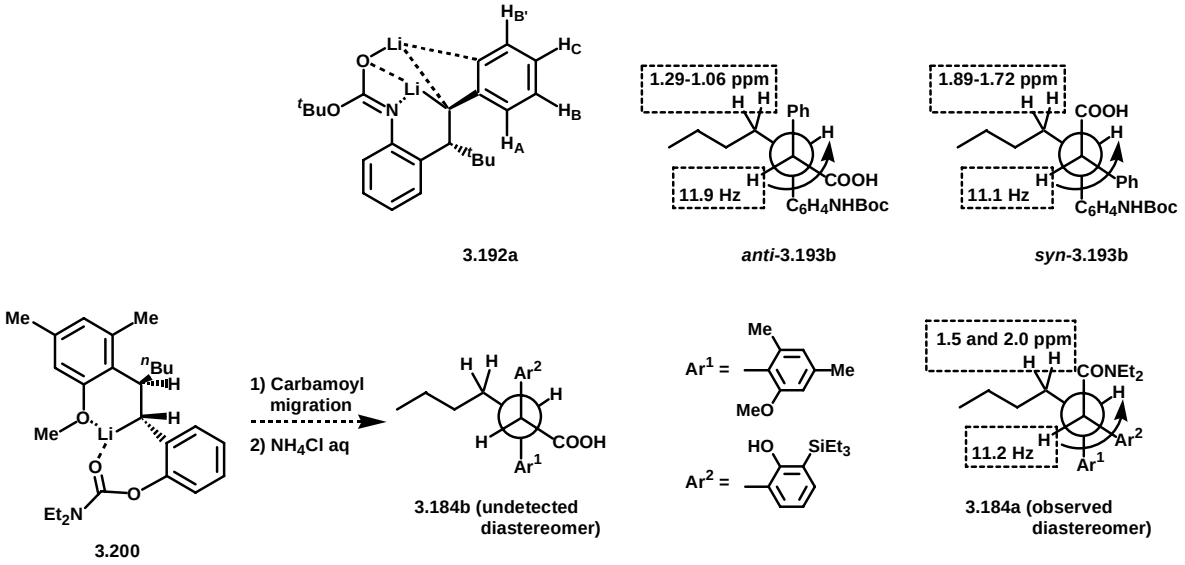
Stilbene	R^1	R^2	Carbolithiated Intermediate	E	Product	Yld (%)	dr
3.191a,b	Boc, Bn	^{t}Bu, ^{s}Bu, ^{n}Bu, Et	3.192	H	3.193	33-87	---
3.191a,b	Boc, Bn	^{t}Bu, ^{n}Bu, Et	3.192	D	3.193-d_1	61-85	95:5
3.191a	Boc	^{t}Bu	3.192a	COOH	3.193a	78	95:5
3.191a	Boc	^{n}Bu	3.192b	COOH	3.193b	56	50:50
3.191b	Bn	^{t}Bu	3.192c	COOH	3.193c	64	60:40



Scheme 3.36

The diastereoselectivity of the latter processes was not studied; however, deuteration of **3.192** has shown that the carbolithiation of **3.191a,b** with all BuLi isomers and EtLi occurs with high *anti* diastereoselectivity (Table 3.1). ^{1}H NMR and gCOSY spectra in THF-d_8, prior to electrophilic quench of the reaction mixture, suggest the presence of only one lithiated species (**3.192a**, Scheme 3.37) whose conformation around certain

bonds appears to be restricted (H_B and $H_{B'}$ are magnetically non equivalent) presumably by a heterochelated ring. Surprisingly, unlike with its ^{t}Bu-isomer **3.192a**, quench of the ^{n}Bu-carbolithiated intermediate **3.192b** with CO_2 (Table 3.1) results in the complete loss of diastereoselectivity and the generation of ***anti*-3.193b** and ***syn*-3.193b** in approximately 1:1 ratio. In our case, ^{1}H NMR analysis of the product mixture obtained from **3.113** showed the presence of only one product (**3.184a**) whose stereochemistry, as determined by X-ray diffraction analysis (Fig. 3.7), may be explained by a *syn*-addition of ^{n}BuLi to **3.113** (Mechanism B). A comparison of the data obtained for ***syn*-3.193b** and **3.184a** shows that, in the crystalline state, both adopt a conformation with *gauche* aryl rings (Scheme 3.37). Furthermore, their ^{1}H NMR display similar $C_\alpha H$-$C_\beta H$ coupling constants (J = 11.1 and 11.2 Hz, respectively) and low field signals for the $CH_3(CH_2)_2CH_2$ protons (δ=1.5 to 3.0 ppm) probably due to the deshielding effect of the nearby CO_2H and $CONEt_2$ groups respectively, which is absent in ***anti*-3.193b**.



Scheme 3.37

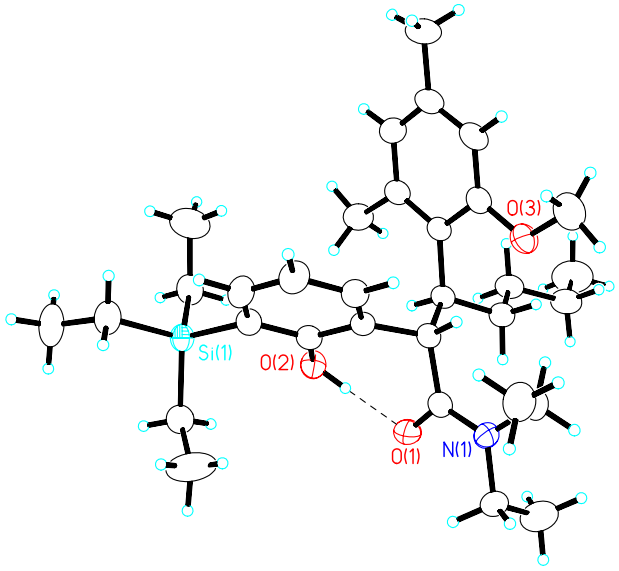
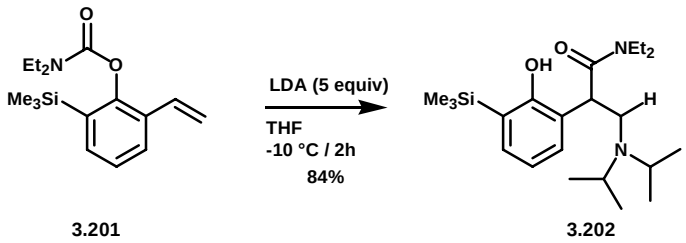


Figure 3.7 Crystal Structure of Dihydrostilbene 3.184a

The high but opposite regio- and diastereoselectivity observed in the formation of **3.184a** compared to that of **3.193** is difficult to rationalize by the carbolithiation mechanism B: the formation of a single lithiated intermediate **3.200** (Scheme 3.37), analogous to **3.192a**, requires a chelation involving the poorly coordinating MeO group and would, in any case, furnish the undetected compound **3.184b**. On the other hand, regioselective formation of **3.184a** appears fully explained by mechanism A. Thus, as already established by Reed, initial α-vinyl deprotonation of **3.113** is followed by rearrangement to **3.183** or **3.112a** which undergo ^{n}BuLi addition and *anti* protonation in the formation of the favoured diastereoisomer **3.184a**. Despite the possible expectation for a direct attack of the strongly nucleophilic RLi reagent on the amide functionality of **3.112a** (masked in the carbinolamine **3.183**), the second step of this sequence is consistent with earlier evidence that tertiary crotonamides undergo rapid Michael addition of alkyl-, vinyl-, and

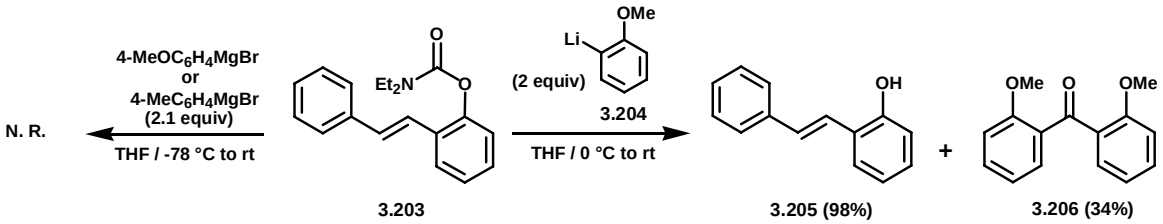
aryllithium reagents and their resulting enolates may be quenched with electrophiles in good yields.[61] In fact, while primary and secondary *trans*-cinnamides are known to undergo preferential ^{n}BuLi nucleophilic α-attack ("3,4 attack" or "contra-Michael"), tertiary *trans*-cinnamides react solely according to the 1,4 mode.[62] A closely analogous reaction to that of **3.113** (Scheme 3.34) is the LDA-mediated conversion of *O*-carbamoyl styrene **3.201** to phenylacetamide **3.202** (Scheme 3.38) for which a mechanism involving alpha-deprotonation-carbamoyl migration followed by Michael addition or, *vice versa* (the result of the first step of an intramolecular Baylis-Hillman reaction) was proposed.[63]



Scheme 3.38

Clearly, if mechanism A is operative, the competition between the slower anionic cyclization of **3.112a** (Scheme 3.15) and the faster Michael addition of ^{n}BuLi suggests that the reaction may benefit from the use of bulky alkyllithiums, equally capable of selectively deprotonating the α-vinyl position of **3.112a**. To place this notion to the test, compound **3.113** was treated with ^{s}BuLi and ^{t}BuLi but gave products analogous to **3.184a**, although these reactions were not as clean as those involving ^{n}BuLi. In a further test, mesityllithium was shown of insufficient basicity to deprotonate the substrate which, even after prolonged stirring at rt, remained intact and was quantitatively recovered. The remarkable stereoselectivity of the conversion **3.113** → **3.184a** encouraged a further glance at this process in an attempt to expand its scope. A preliminary investigation intended to involve synthetically useful aryl Grignard reagents showed no reactivity

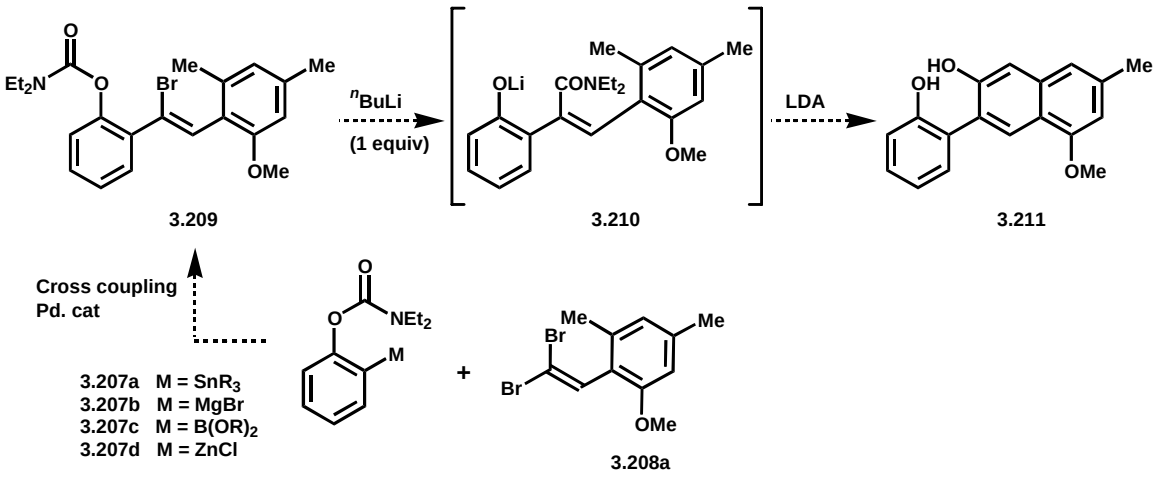
towards the simple stilbene **3.203**. Similarly, *ortho*-anisyllithium did not effect deprotonation of **3.203** *ortho* to the carbamate group nor at its α-vinyl site. This was somewhat expected on the basis of the previous experiment with mesityllithium; however, due presumably to its lower hindrance, *o*-anisyllithium attacked the carbamate group resulting in its quantitative cleavage to give **3.205** (98%) together with expected benzophenone **3.206** (34%, based on **3.203**, Scheme 3.39).



Scheme 3.39

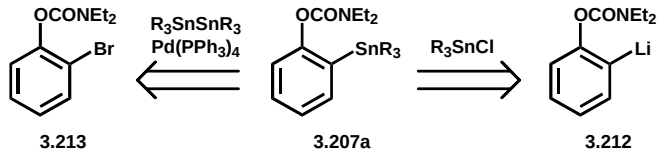
3.3.5. Synthesis of α-Bromo Carbamoyl Stilbene 3.209

In a different approach, selective generation of the α-vinyl anion **3.113** (Scheme 3.15) was considered by a metal-halogen exchange reaction on the vinyl bromide **3.209** (Scheme 3.40). Owing to the high rate of metal-halogen exchange reactions,[64] no carbolithiation was expected to occur upon treatment of **3.209** with stoichiometric amounts of ^{n}BuLi. For the same reason, no D*o*M reaction was anticipated on the DMG-bearing ring; hence the non *o*-silylated substrate **3.209** was tested in this approach. Arguably, the best route to bromide **3.209** with the required *Z* stereochemistry is the stereoselective cross coupling of *gem*-dibromostyrenes **3.208a** (Scheme 3.40). This reaction is based on the known rate difference in the Pd-catalyzed cross coupling of (*E*)- and (*Z*)-1-bromo-1-alkenes[65] and has been carried out with alkenylzirconiums[66] as well as under Kumada,[67] Stille,[68] Suzuki[69] and Negishi[70] conditions.



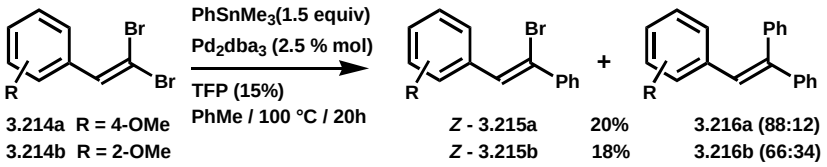
Scheme 3.40

The Stille reaction was initially neglected due to safety concerns over the large scale use of highly toxic chlorotrialkyl- or hexaalkyldistannane[71] required to obtain bulk amounts of the coupling partner **3.207a** (Scheme 3.41).



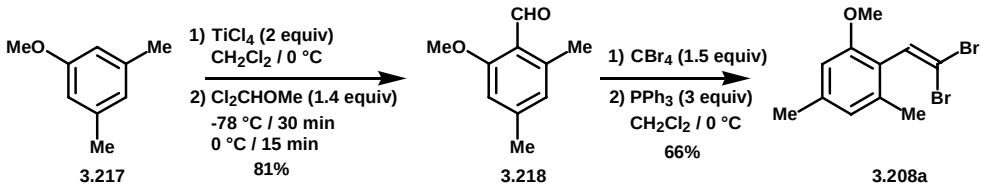
Scheme 3.41

Furthermore, Shen has shown that *ortho*- and *para*-methoxy *gem*-dibromostyrenes do not undergo efficient coupling with trimethylphenyltin, most likely due to the conjugative donating effect of the methoxy groups that decelerates the Pd(0) oxidative addition into the C-Br bond (Scheme 3.42). The Kumada conditions (**3.207b** in refluxing ether, Scheme 3.40) were also discarded due to their incompatibility with the carbamoyl group of the Grignard reagent which would have rapidly undergone the anionic *o*-Fries rearrangement and would have failed to participate in the cross coupling reaction.



Scheme 3.42

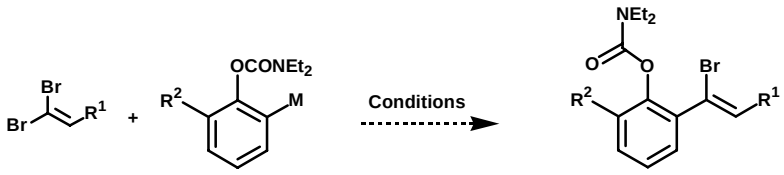
In pursuit of a solution, the commercially available 3,5-dimethylanisole was subjected to electrophilic aromatic formylation under conditions that selectively provided **3.218** together with minor amounts of the other possible regioisomer (Scheme 3.43).[72] The Ramirez protocol[73] for the Wittig-type dibromoolefination of **3.218** gave the 1,1-dibromostyrene **3.208a** (66%) whose coupling was tested under the conditions established by Minato (Negishi coupling) and Shen (Suzuki coupling).



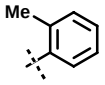
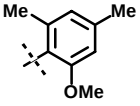
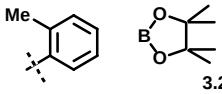
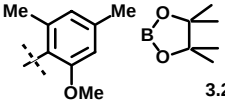
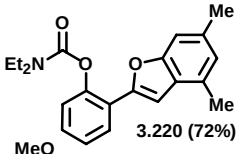
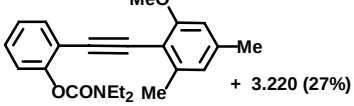
Scheme 3.43

In the best case, the Negishi reaction of the simple dibromide model **3.208b** yielded a mixture of inseparable products whose GC-MS analysis showed no presence of the desired product **3.209** (Entry 1, Table 3.2). A more complex mixture was obtained when the trisubstituted dibromostyrene **3.208a** was subjected to the same conditions (Entry 2). The more widely generalized Suzuki coupling appeared to offer higher hopes of success through the application of the experimental conditions optimized by Shen (Entry 3).

Table 3.2 Attempts at Regioselective Cross Coupling of *gem*-Dibromostyrenes 3.208a,b with Arylmetalloids 3.207

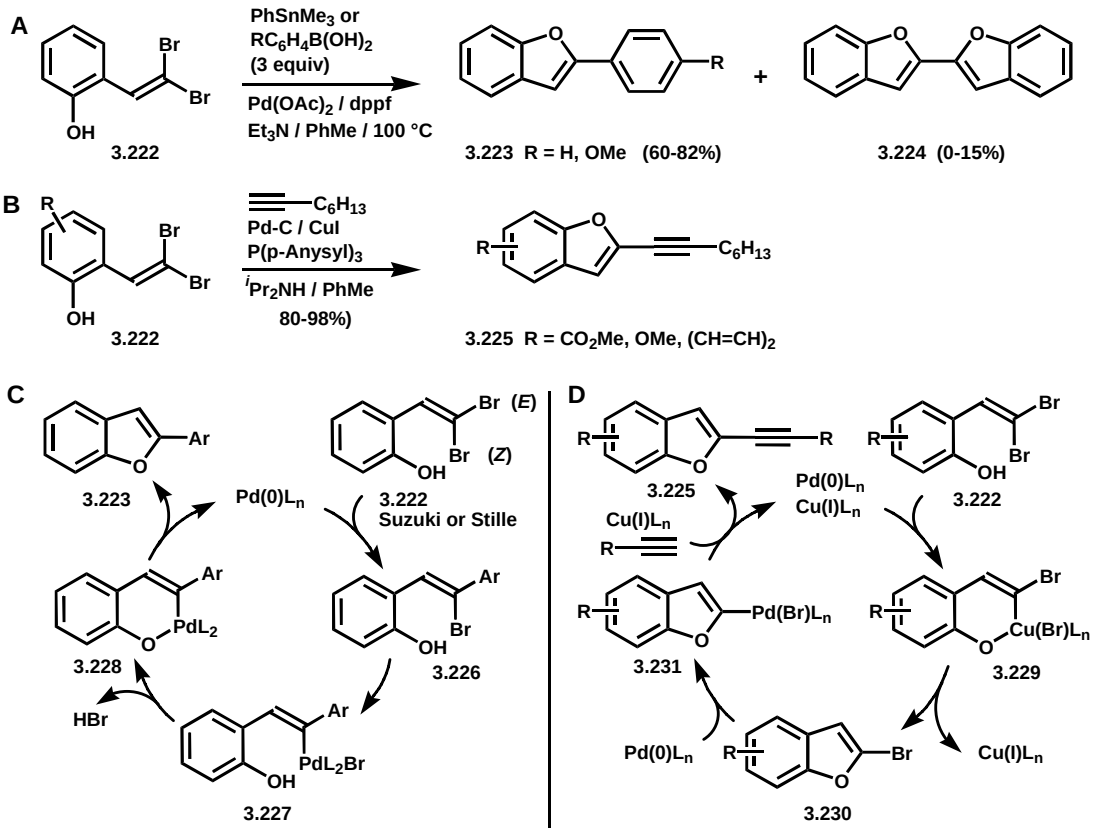


3.208 3.207 3.219

Entry	R^1	M	R^2	Conditions	Products
1	 3.208b	ZnCl 3.207d	H	$Pd_2(dba)_3$ (0.75%) dppb (1.5 %) THF / 0 °C to rt / 12h	Unseparable mixture of unidentified compounds
2	 3.208a	"	H	$Pd_2(dba)_3$ (0.75%) dppb (1.5 %) THF / 0 °C to rt / 12h	Complex mixture
3	 3.207e		TMS	$Pd_2(dba)_3$ (2.5%) tri(2-furyl)phosphine (15 %) Na_2CO_3 / Dioxane / 65 °C / 12h	N.R.
4	 3.207c		H	$Pd_2(dba)_3$ (2.5%) tri(2-furyl)phosphine (15 %) Na_2CO_3 / TBAF (1 equiv) Toluene / 80 °C / 12h	 3.220 (72%)
5	"	"	H	$Pd(PPh_3)_4$ (10%) Tl_2CO_3 (2 equiv) THF / H_2O / rt/ 6h	 + 3.220 (27%) 3.221(24%)
6	"	"	H	$Pd(PPh_3)_4$ (10%) $Ba_2(OH)_2$ (2 equiv) THF / MeOH / rt/ 12h	3.221 (47%)
7	"	"	H	$Pd_2(dba)_3$ (1%) S-Phos 2% / K_3PO_4 toluene, 65-120 °C	N.R.

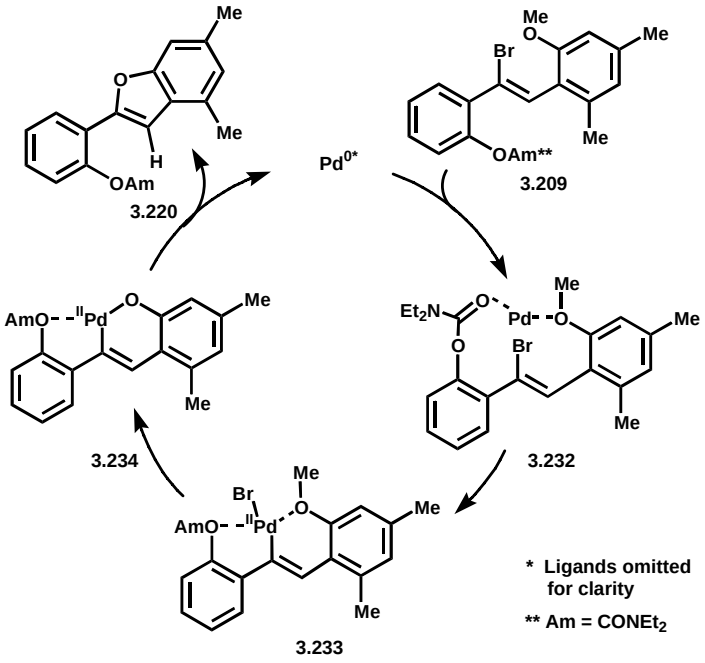
These high expectations were met with disappointment when the mixture blackened and the partners were recovered mostly unreacted. Although superseded by Shen's optimized conditions, the addition of TBAF has also been reported to greatly improve the outcome of this type of reaction run in toluene. Thus, TBAF, other bases ($Ba(OH)_2$, Tl_2CO_3), and solvents (toluene, THF, DMF) were tested following isolated published examples of similar couplings involving vinylboronate partners.[74] As observed by Shen, TBAF is critical to the progress of the reaction, often leading it beyond the formation of the

desired product to the bis coupled derivative. However, when coupling **3.208a** with **3.207c** (entry 4) the product of the reaction was not a doubly arylated product but, unexpectedly, the phenylbenzofuran **3.220**. Highly toxic[75] and no longer commercially available Tl(OH), reported to give excellent yields in the selective coupling of alkenylboronic acids,[74a,b] was generated *in situ* from Tl_2CO_3 and was also found to give **3.220** together with the internal alkyne **3.221** (Entry 5). **3.221** was observed as the major product when $Ba(OH)_2$ was used as the base (Entry 6). Finally, the generally efficient S-Phos ligand did not promote the coupling reaction and led to partial recovery of starting material (79%). Further work on this reaction was not carried out since this transition metal-catalyzed synthesis of benzofurans from hydroxylated gem-dibromostyrenes had been reported in 2004 (Scheme 3.44, Reaction A)[76] and recently applied by Lautens to the preparation of alkynylbenzofurans (Reaction B).[77] In the case of the synthesis of **3.225**, there is evidence suggesting that Cu catalysis is responsible for the formation of bromobenzofuran **3.230** which then undergoes coupling according to the Sonogashira mechanism (Mechanism D). In the absence of Cu salts,[78] the coupling at the (*E*)-brominated position has instead been considered to be the initial step of this reaction (Mechanism A). The furan ring is thus formed through a sequence of steps (Pd-oxidative addition to the (*Z*) C-Br bond of **3.226**, HBr elimination from **3.227** and reductive elimination of **3.228**) which does not include the transmetalation of a second molecule of $PhSnMe_3$ to **3.227**.

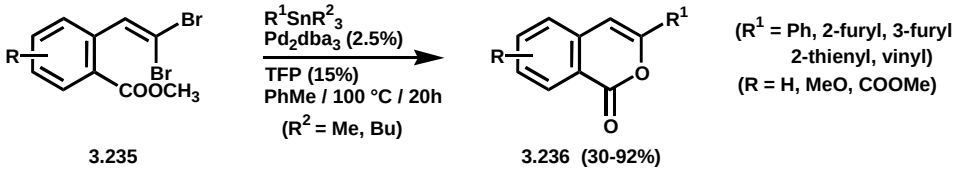


Scheme 3.44

Whatever the order of the coupling steps may be, a working mechanism for the formation of **3.220** must include a dealkylation step leading to the palladacycle **3.234** which, upon reductive elimination, ejects benzofuran **3.220** (Scheme 3.45). Thus, bromostilbene **3.209**, following chelation of the catalyst, undergoes palladium oxidative addition to give **3.233** which, through HBr elimination, converts to **3.234** and finally undergoes ring contraction to benzofuran **3.220**. Albeit unusual, dealkylative events like these, presumably due to the Lewis acidity of the Pd(II) species formed in the catalytic cycle,[79] have been invoked by Heck[80] and reproposed by Shen in a similar tandem reaction yielding 3-vinyl and 3-aryl isocumarins **3.236** (Scheme 3.46).[81]



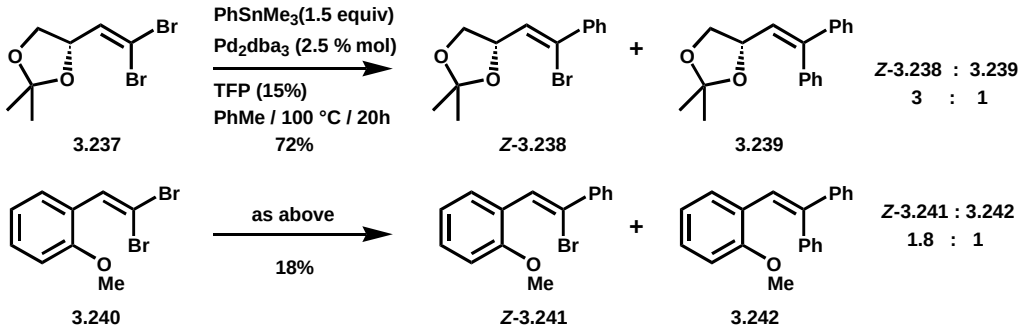
Scheme 3.45



Scheme 3.46

Attempts to effect coupling reactions of **3.207c** and **3.208a** (Table 3.2) at lower temperatures did not yield even traces of **3.209**, suggesting that the latter is rapidly consumed as it is formed under the reaction conditions. It is plausible to suggest that the carbamate group of **3.232** (Scheme 3.45) may act in concert with the methoxy group in the coordination of palladium(0), significantly accelerating the second oxidative insertion by Pd(0) into the C-Br bond (**3.233**). The coordinative effect (CIPE) of an alkoxy group on the rate of Pd(0) oxidative addition has been stressed by Shen to rationalize the formation, under Stille conditions, of relevant amounts of diphenylated products **3.239**

and **3.242** (Scheme 3.47). Since biarylated species were not observed when **3.208a** was subjected to any of the tested coupling conditions (Table 3.2), the results may be rationalized by consideration that **3.233** must undergo dealkylation and subsequent reductive elimination more rapidly than transmetalation with a second equivalent of the arylboronic ester **3.207c** (Scheme 3.45).

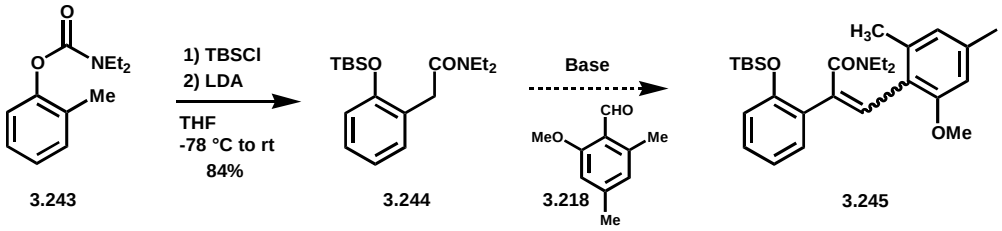


Scheme 3.47

3.3.6. Alternative Approaches to a Suitable Cinnamide

Despite the lack of satisfactory hypotheses on the possible reaction pathways leading to the extensive LDA-triggered decomposition of the carbamoyl stilbenes discussed above, the time appeared mature to explore alternative routes towards the cinnamide **3.112b** that did not include the carbamoyl translocation reaction (Scheme 3.15). The non-stereoselective methods include the classical Knoevenagel-type condensation of phenylacetamide **3.244** with the benzamide **3.218** (Scheme 3.48). Starting material **3.244** may be obtained in one step by treatment of tolyl-*O*-carbamate **3.243** with TBSCl and LDA by the Kalinin protocol,[82] in which the *in situ* presence of TBSCl is necessary to prevent intermolecular reactions involving the benzylic position; upon silylation of the benzylic position followed by carbamoyl lateral migration, the intermediate undergoes a Brook-type rearrangement[83] to give a useful *O*-protected phenylacetamide **3.244**.

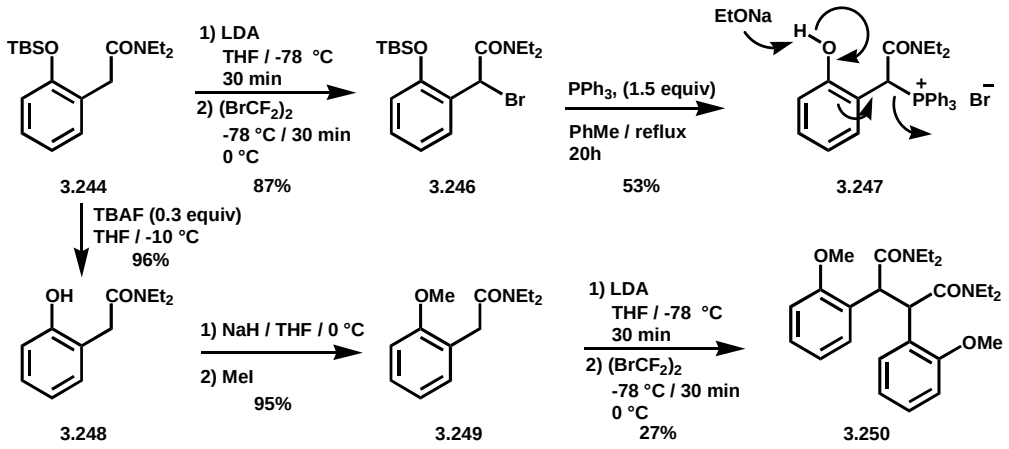
Perhaps unsurprising under the standard weakly basic Knoevenagel conditions (piperidine/reflux in pyridine), no reaction was observed; however, using the stronger LDA or ^{n}BuLi, compound **3.244** was easily deprotonated as demonstrated by a $(BrCF_2)_2$ quench (see Scheme 3.49), but proved stubbornly unreactive towards the highly hindered benzaldehyde **3.218**.



Scheme 3.48

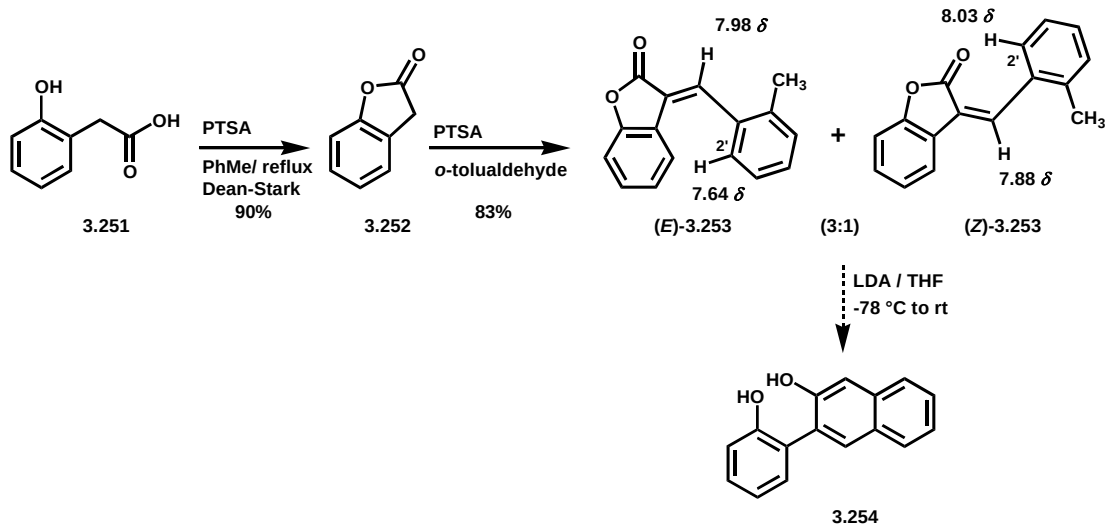
Next, a Wittig approach was placed to the test to prepare **3.245** (Scheme 3.49). Thus, anionic bromination of **3.244** yielded **3.246** in 87% yield. However, reaction of the latter with PPh_3 occurred only at the expenses of the silicon protection, giving **3.247** in 53% yield. When exposed to EtONa to obtain the corresponding ylide, **3.247** ejected PPh_3, suggesting the need for the installation of a more robust protection group on the phenolic group. To this end, the silicon protection group of **3.244** was efficiently removed with substoichiometric amounts of TBAF (0.3 equiv) to give **3.248**, which was protected as the methyl ether **3.249** in 95% yield. However, the synthesis of the α-bromo derivative of **3.249**, analogue to **3.246**, by treatment with LDA followed by quench with an effective Br^+ reagent,[84] was heavily affected by the formation of a dimeric product (**3.250**) in 27 % yield. This result is possibly due to the formation of the α-bromo intermediate followed by S_N2 bromide-displacement by the α-lithiated derivative of **3.244**. The observation that the PMB ether of **3.248** displays identical reactivity while the more hindered **3.244** undergoes smooth bromination supports the hypothesis of a polar reaction. The coupling

of enolates of carboxylic acid derivatives is also known to occur through oxidation of the enolate to a radical by a single electron transfer (SET) process. However, the working mechanism of these radical reactions require the addition of oxidants such as I_2, iodonium salts, Cu(II), Ti(IV)or Fe(III).[85] Surprisingly, reverse addition of α-lithiated **3.249** to Br^+ sources (NBS, $BrCF_2CF_2Br$) still yielded **3.250** as the main product. Radical bromination of **3.249** using AIBN/benzoyl peroxide and NBS[86] efficiently brominated the aromatic ring as clearly indicated by peak integration of the ^1H NMR aromatic region.



Scheme 3.49

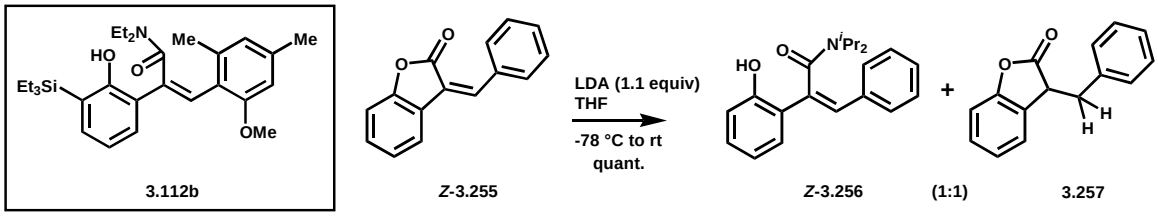
During the course of the above studies, a suitable substrate for the synthesis of the naphthol model **3.254** was recognized in the isoaurone ***Z*-3.253** which was prepared according a known procedure[87] by condensation of benzofuran-2-one (**3.252**) with *o*-tolualdehyde in the presence of catalytic amounts of PTSA (Scheme 3.50). Compound **3.253** was obtained as an inseparable 3:1 mixture of geometric isomers (^1H NMR estimate); unfortunately, overlapping NMR signals in the spectrum of this isomeric mixture prevented the assignment of the correct stereochemistry through NOESY experiments.



Scheme 3.50

However, a perusal of the pertinent literature showed that in virtually all known isoaurones, the olefinic proton of the *E* isomers is diamagnetically deshielded by the carbonyl group and gives a ^{1}H NMR signal about 0.25 ppm downfield of the value given by the *Z* counterparts.[88] Similarly, $H_{2'}$ and/or $H_{6'}$ of the *Z* isomers are strongly deshielded (downfield shift is ~ 0.5 ppm) compared to the corresponding hydrogens of the *E* isomers. Based on this criterion of assignment, validated by other NMR techniques,[88d, 89] the isomeric mixture of **3.253** was identified as a 3:1 *E*:*Z* mixture, in which the unwanted isomer was predominant. *E*/*Z* mixtures of isoaurones have been resolved, not without failures, by repeated recrystallization or by fractional distillation. When the isomeric mixture of ***E***- and ***Z***- **3.253** was subjected to distillation, it was enriched to a 20:1 *E*/*Z* mixture. Both the 3:1 and the 20:1 *E*/*Z* mixtures of **3.253** were subjected to LDA at −78 °C in the hope that the base would generate the desired geometric isomer through reversible 1,4 nucleophilic addition of LDA to the α,β-unsaturated lactone. However, in both cases, while undergoing highly exothermic reaction with the base at −78 °C, the yellow THF solution of **3.253** became deep red and rapidly blackened even at

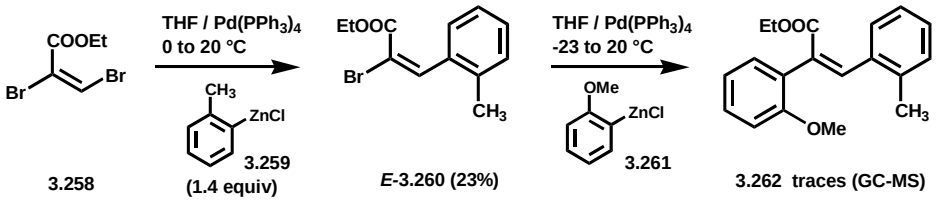
temperatures as low as −78 °C. Only starting material (11%) could be recovered from the complex mixture obtained. The more hindered LiTMP gave an equally complex mixture. Curiously, when the known unsubstituted isoaurone ***Z*-3.255**, isolated in pure form, was exposed to LDA, no complex reactivity was observed, but the substrate quantitatively underwent nucleophilic ring opening (**3.256**) and double bond reduction (***Z*-3.257**) in a 1:1 ratio (Scheme 3.51).



Scheme 3.51

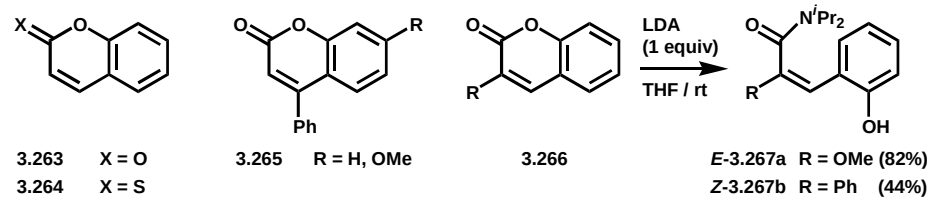
This result suggests that an LDA-mediated and rapid reaction (−78 °C) involving, once again, the methyl group of **3.253** (Scheme 3.50) interferes with the cyclization of the *Z* isomer. Could the unexpected and obscure reactivity of **3.253** also apply to the structurally related cinnamide **3.112b**? To rule out such a possibility that appeared to undermine the success of the whole project, a stereoselective synthesis of a *cis* 2'-methyl cinnamic ester or amide was pursued. *Cis* α-aryl cinnamates have been prepared by sequential cross coupling of *trans*-dibromoacrylate (**3.258**, Scheme 3.52**)** with several arylzinc species.[90] The reaction succeeds because the β-bromo substituent of **3.258,** under Pd-catalyzed Negishi and, in some cases, Stille conditions, undergoes cross coupling at a faster rate than the corresponding α-bromo substituent. In potential application of these results, *ortho*-tolylzinc chloride **3.259** was first subjected to cross coupling with dibromoacrylate **3.258**. Although the reported conditions did not afford a

trace of product, it was found that premixing of the catalyst with the dibromide was critical to the observation of ***E*-3.260** formation. Gradual addition of a small excess of **3.259** (1.4 equiv) resulted in the disappearance of the starting material and led to the formation of ***E*-3.260** albeit only in 23% yield. The low isolated yield of ***E*-3.260** and its even poorer coupling with *ortho*-anisylzinc chloride to give **3.262** suggested halting this approach.



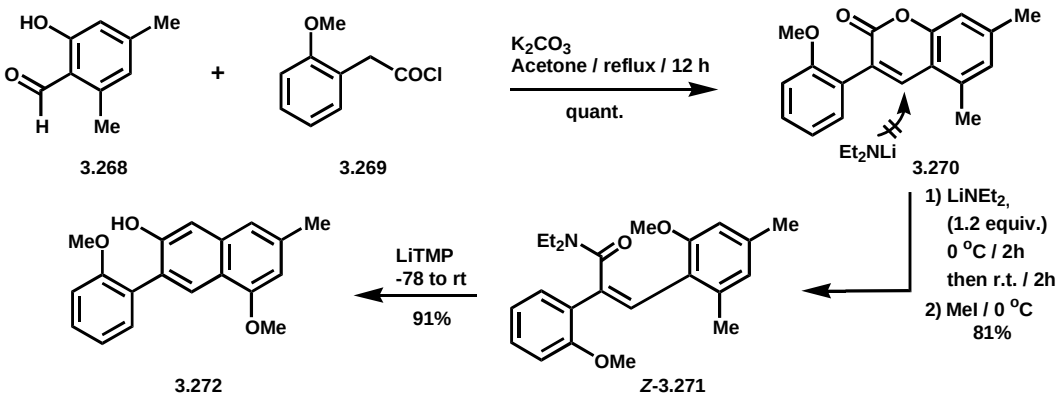
Scheme 3.52

Eventually, a successful synthesis of a suitable *cis*-cinnamide was achieved using conventional chemistry. Dr. Jignesh Patel, a post-doctoral fellow in our group who at this point joined in this work, brought the attention to a report describing the behaviour of coumarins when subjected to treatment with LDA.[91] This study showed that, although coumarin (**3.263)**, thiocoumarin **3.264** and 4-phenyl coumarins **3.265** give complex mixtures of products, 3-substituted coumarins **3.266** do not undergo lithiation at C_4 but, rather, ring opening to give the corresponding cinnamides **3.267a,b** in variable yields (Scheme 3.53).[92]



Scheme 3.53

To test this approach to a new DreM methodology for the requisite biaryl **3.272**, **3.270** was prepared in quantitative yield through esterification of the known salicylaldehyde **3.268** with **3.269** followed, *in situ*, by intramolecular Knoevenagel condensation of the arylacetate intermediate (Scheme 3.54).[93] The synthesis of a diethyl *cis*-cinnamide corresponding to **3.112b** (Scheme 3.15) required the opening of the lactone ring of **3.270** with Et_2NLi, which presented the risk of a competitive 1,4 Michael addition (Scheme 3.54). The latter reaction may be discouraged with the use of the hindered LDA; however, the isopropyl analogue of ***Z*-3.271** which would be generated was expected to undergo a more sluggish cyclization to naphthol **3.272** on account of the steric hindrance.



Scheme 3.54

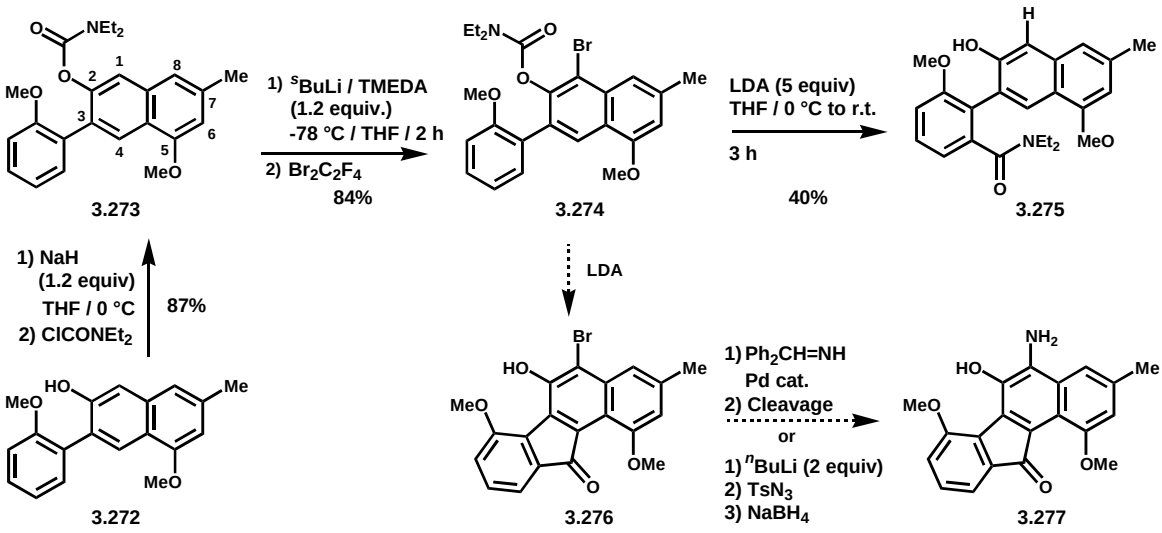
Fortunately, the undesired Michael addition of $LiNEt_2$ to **3.270** was not observed and the lactone ring opening followed by *in situ* trapping of the phenolate intermediate as a methyl ether, afforded only the ***Z*-3.271** in 81% yield. The advantage of this methodology lies in the fact that the *Z* geometry of the product is obligatorily set in the starting coumarin and is not modified during the reaction even though such a possibility exists by reversible Michael addition-elimination of the base to the product. The cinnamide ***Z*-3.271** was then treated with LiTMP under a variant of the standard DreM

conditions[94] and led, to our delight, to the key naphhtol **3.272** in high yield (91%). This result strongly suggests that the observed complications of the $O \rightarrow \alpha$ vinyl carbamoyl migration are responsible for the unsatisfactory results of the anionic cascade (Scheme 3.22).

3.3.7. Construction of the Benzo[*a*]fluorenone Skeleton

As a sole investigator, Patel surveyed the potential modifications that may set up the naphthol **3.272** towards a successful sequence of DreM reactions.[95] The carbamoylation of the naphthol **3.272** to **3.273** (87%, Scheme 3.55) provided the opportunity of effecting the original plan to attempt the *ortho*-amination of a naphthalene ring for the purpose of testing the following DreM reactions through which the B ring is formed (Scheme 3.15). However, in order to avoid the protection of the amino group required during the sequence of DreM reactions, it was decided to postpone the amination of **3.273** to the conclusion of all anionic chemistry. The C_1-protection of **3.273**, an obligatory step before attempting the DreM reaction, was undertaken by metalation-bromine quench and the corresponding temporary TMS protection, both potentially instrumental in the later installation of the amino group. In the first scenario (Scheme 3.55), amination was considered to rely on Buchwald's protocol,[96] which would require cross coupling of the bromide **3.276** with benzophenone imine and cleavage of the resulting product to give **3.277**. Alternatively, **3.276** would be subjected to metal-halogen exchange followed by TsN_3 quench and reduction of the azide obtained to give **3.277**. Although the reaction of LDA with bromoarenes (**3.274** → **3.276**) is fraught with the problem of elimination to benzyne species,[97] the absence of β-hydrogens to the bromo substituent in **3.274** granted probability of success. In pursuit of this goal, carbamate **3.273** was metalated and

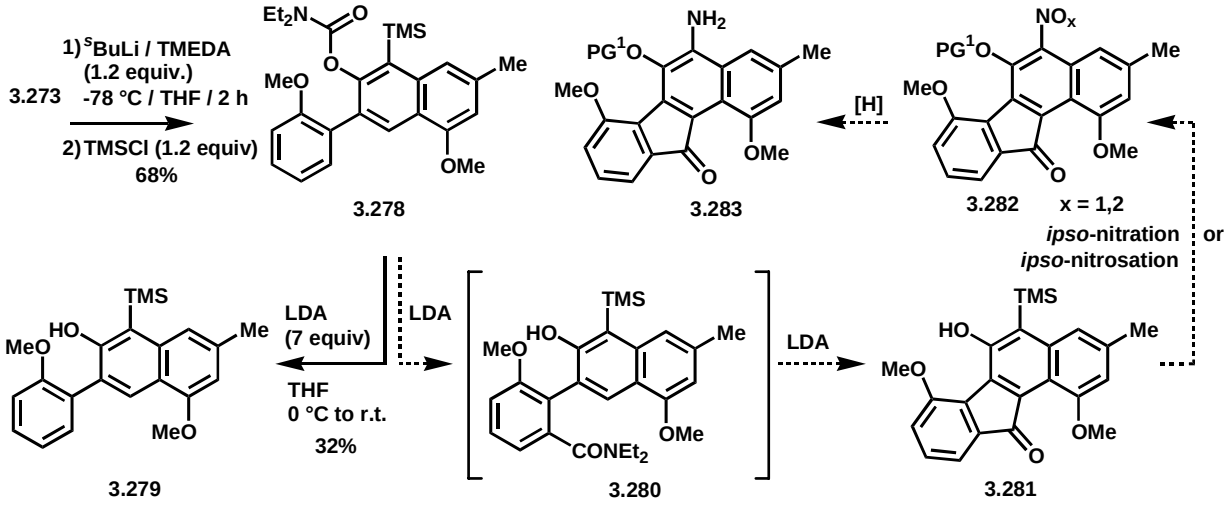
brominated to give **3.274** in 84% yield. Sadly, when **3.274** was subjected to DreM conditions, the resulting product **3.275** obtained in modest yield, showed that, although carbamoyl migration had occurred, it was accompanied by a reductive debromination. Although, to the best of our knowledge, such a reaction is unprecedented for LDA, it may have occurred through a mechanism similar to the metal-halogen exchange reaction involving alkyllithiums. If so, the reductive cleavage must have occurred after the migration of the carbamoyl group to the alternate ring, or else an *ortho*-Fries rearrangement would have been observed. This process may be envisaged as mediated by the phenolate group which may play role in the coordination of the base and in the stabilization of the generated *ortho*-lithiated species.[98]



Scheme 3.55

The 2-silylation of **3.273** (Scheme 3.56) with the robust TMS group[99] to the derivative **3.278** appeared a reasonable alternative to the unsuccessful rearrangement of **3.274**. The TMS group was expected a) to withstand rather well the following DreM (**3.280**), based on Mohri's precedent and b) to activate the α position towards an *ipso*-bromo- or nitro-

desilylation reaction[100] (**3.282**) as a prelude to the preparation of the amino derivative **3.283**. Once again, however, we were disappointed to observe that **3.278**, obtained through D*o*M of **3.273** in 68% yield, suffered cleavage of the carbamate group on contact with LDA (**3.279**, 32 %) and gave a more complex mixture of products when exposed to the bulkier LiTMP.



Scheme 3.56

Due to the centrality of the DreM reaction in this project and convinced of the critical role that it may play in the construction of ring B, Patel is now exploring other suitable substrates that may effectively undergo the combined remote carbamoyl migration – DreM and cyclization. Once a suitable fluorenone (*e.g.*, **3.283**) becomes available, the last strides to the target molecule will focus on the manipulation of the substituents which draw from precious results of Dmitrienko and many others who have optimized the last synthetic steps to prekinamycin (Schemes 3.5 and 3.6)[9,30] and kinamycins (Schemes 3.9-3.11).[25-27]

3.4. Future Work

The failure of **3.278** (Scheme 3.56) to undergo the single or double DreM reaction to products **3.280** and **3.281**, respectively, as in Kendall's case (**3.177**, Scheme 3.33) is difficult to rationalize. The structure **3.278** (Fig. 3.8) does not show remarkable steric hindrance that may prevent the operation of a CIPE,[55] especially when compared to other structurally related substrates which have successfully undergone a DreM reaction (**3.176**, **3.284**-**3.286**, Fig. 3.8). While the remote lithiation of **3.176**[31] may have been facilitated by the presence of the C_7-OMe group, this synergistic combination of directing effects is not a general requirement of the DreM reaction (compare with **3.284**,[50] **3.285**[50] and **3.286**[49]). DFT calculations are now being carried out on **3.278** and **3.176** to gain some perception of the intra- and intermolecular interactions that may prevent a productive coordination of the base with the carbamate group and the remote hydrogen.[101]

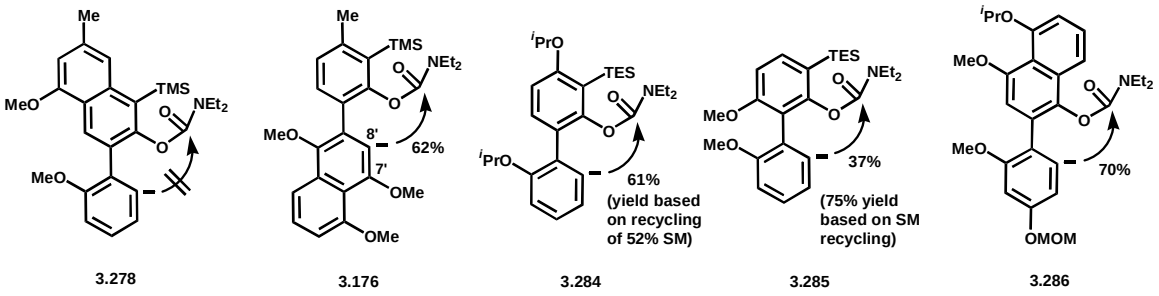
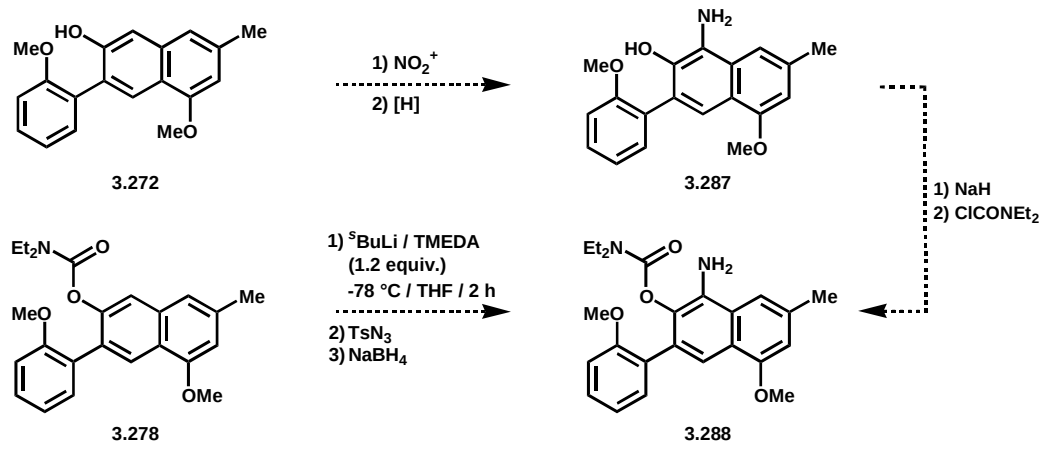


Figure 3.8 Some Known Examples of DreM of 2-Aryl-2-*O*-Carbamoyl Arenes

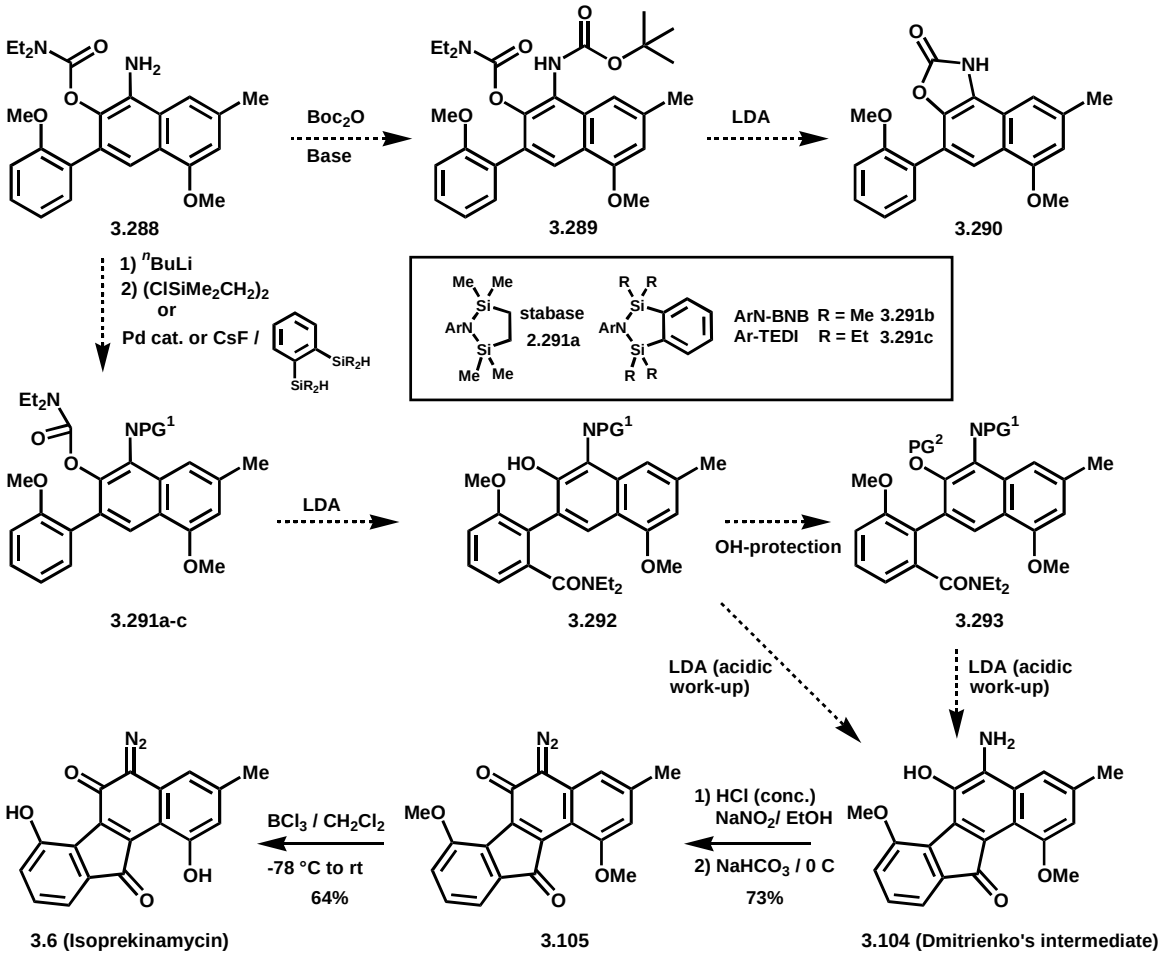
The original plan involving the early *ortho*-amination of **3.110** (Scheme 3.15) is yet to be tested. This functionalization may be achieved by electrophilic nitration/reduction of the naphthol **3.272** or, should the nitration occur with poor regioselectivity, by applying the Snieckus D*o*M protocol using a TsN_3 quench – borohydride reduction sequence (**3.278** → **3.288,** Scheme 3.57).[102]



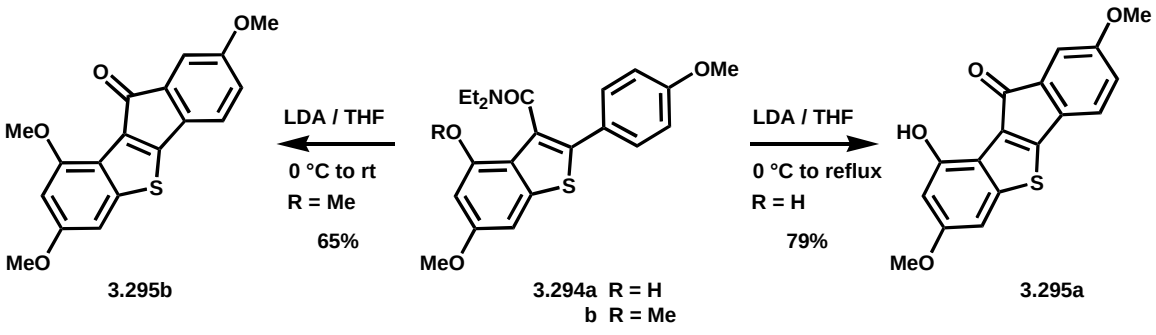
Scheme 3.57

The protection of the amino group as *N*-Boc (**3.289**, Scheme 3.58), a common practice in anionic aromatic chemistry, might complicate the following DreM reaction with the occurrence of a transamidation reaction leading to the cyclic carbamate **3.290**. In this event, this problem may be overcome by the use of *in situ* primary amine protection as offered by "stabase" derivatives like **3.291a** which are stable to LDA and promptly hydrolyze on acidic quench (0.1 N HCl).[103a] On the other hand, "benzostabase" and TEDI derivatives like **3.291b** and **3.291c** respectively (Scheme 3.58) have been reported to display good and excellent stability, respectively, to silica gel chromatography.[103b,c] This property may be providential in the case that, as experienced by Mohri (Scheme 3.7),[31] OH-protection of the intermediate **3.292** may be required for the second DreM reaction to proceed, therefore implying further purification steps. On the other hand, during the synthesis of a constrained analogue of Raloxifene, Kalinin and coworkers found that the hydroxybenzothiophene **3.294a** (Scheme 3.59) underwent DreM reaction to **3.295a** in higher yield than did its methyl ether **3.294b** to give **3.295b**.[104] This suggests that a tandem DreM reaction, followed by a mild acidic work-up to hydrolyze the *N*-protective group,[103c] may indeed effect the conversion of **3.291** directly into

Dmitrienko's intermediate **3.104** towards **3.6** (Scheme 3.58) thereby concluding the synthesis of isoprekinamyicn.



Scheme 3.58

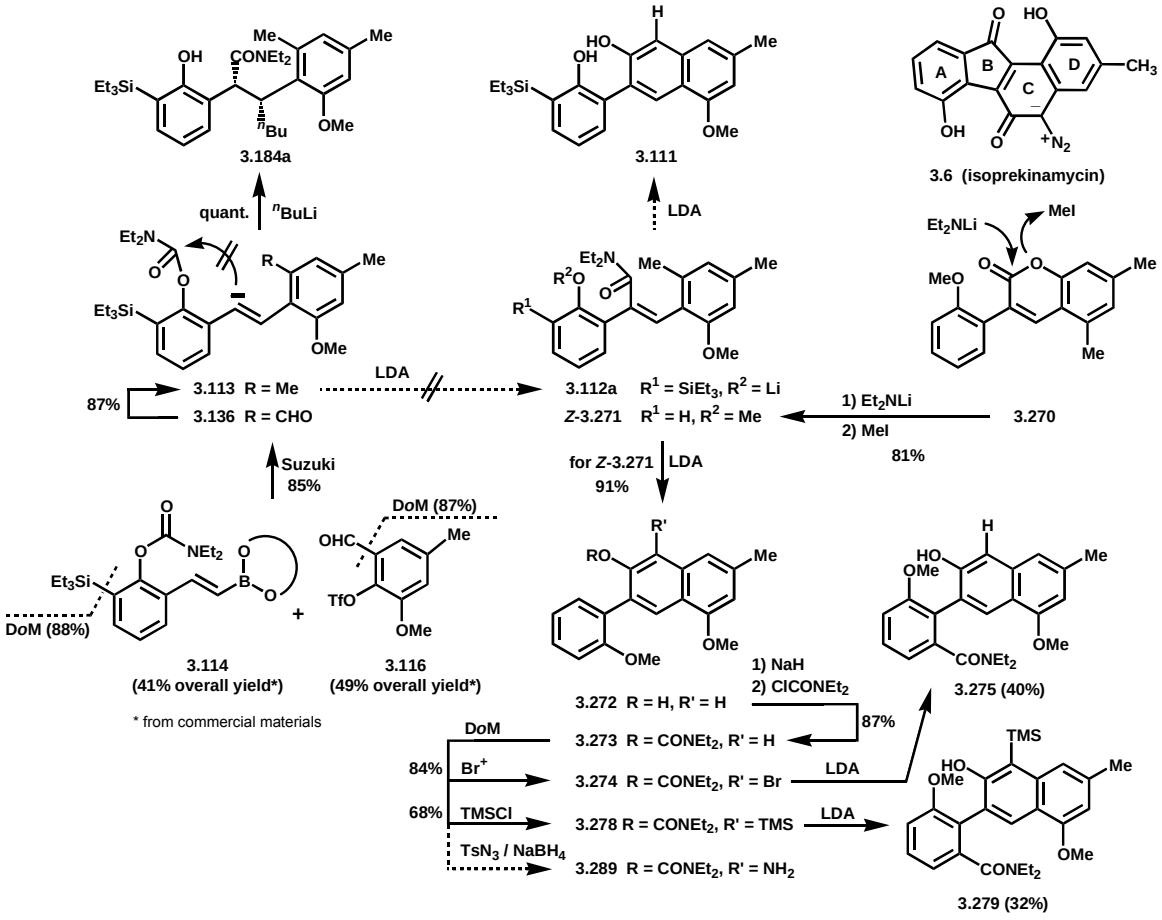


Scheme 3.59

3.5. Conclusions

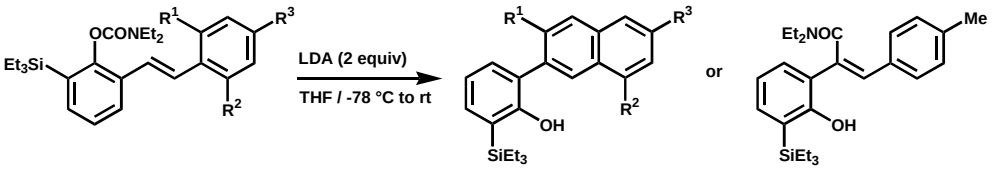
Following the discovery of the anionic $O\rightarrow\alpha$ and β vinyl carbamoyl translocation of 2-(*O*-carbamoyl) stilbenes by Reed (Scheme 3.17) and based on Mohri's successful precedent in the synthesis of tri-*O*-methylkinafluorenone **3.53** (Scheme 3.7), a total synthesis of isoprekinamycin was designed that heavily relies on DoM, DreM and cross coupling chemistry. The key steps of this strategy are a) the synthesis of the AD ring system (**3.113**, Scheme 3.60), b) anionic closure of ring C and c) anionic closure of the five-membered B ring. With respect to point (a), the results show that the coupling partners **3.114** and **3.116** could be prepared by large scale D*o*M reactions (10-30 g, Schemes 3.19 and 3.18 respectively) and, for **3.114**, through a pathway involving an efficient 4-step one-pot reaction. Suzuki cross coupling of these partners smothly gave the stilbene **3.136** which was deoxygenated efficiently to **3.113**. In point (b), attempts to effect the anionic cascade **3.113**→**3.112a**→**3.111** with LDA led to extensive degradation. While still suffering significant decomposition, silylated stilbene derivatives **3.140** and **3.152** were found to give low yields of naphthols **3.143** and **3.153**, respectively (Table 3.3). Although no mechanistic rationale has been envisaged for this chemical behaviour, the low yields of products also obtained upon exposure of the simpler stilbene models **3.168** and **3.171** to LDA strongly suggests that these failures are to be ascribed to the formation of benzylic anions which interfere with the $O\rightarrow\alpha$ carbamoyl translocation step of the anionic tandem reaction (Scheme 3.22). On the other hand, following treatment of **3.113** with ^{n}BuLi, the $O\rightarrow\alpha$ carbamoyl translocation step appeared to occur quantitatively, albeit the presumed intermediate product (**3.112a**) succumbed to 1,4 Michael addition of the alkylithium to give **3.184a** (Scheme 3.60). An inverse

mechanism is also possible that invokes the carbolithiation of stilbene **3.113** followed by *O*→*C* 1,4-migration of the carbamoyl group (Scheme 3.34).



Scheme 3.60

Table 3.3 Chemical Behaviour of Methylated 2-*O*-Carbamoyl Stilbenes upon Exposure to LDA



Stilbene		Naphthol		Detailed Scheme
3.113	$R^1 = R^3 = Me$ $R^2 = OMe$	-----		3.22
3.140	$R^1 = Me$ $R^2 = OMe$ $R^3 = CH_2TBS$	3.143	$R^1 = OH$, $R^2 = OMe$, $R^3 = CH_2TBS$ (30%)	3.23
3.141	$R^1 = R^3 = CH_2TBS$ $R^2 = OMe$	3.144	$R^1 = NEt_2$, $R^2 = OMe$, $R^3 = CH_2TBS$ (24%)	3.23
3.142	$R^1 = CH_2TBS$ $R^2 = OMe$ $R^3 = Me$	-----		3.23
3.152	$R^1 = Me$ $R^2 = OMe$ $R^3 = CH_2TMS$	3.153	$R^1 = OH$, $R^2 = OMe$, $R^3 = CH_2TMS$ (15%)	3.26
3.168	$R^1 = Me$, $R^2 = R^3 = H$	3.169	$R^1 = OH$, $R^2 = H$ (9%)	3.30
3.171	$R^1 = R^2 = H$, $R^3 = Me$		3.172(10%)	3.31

An alternative approach based on the ring opening of coumarin **3.270** (Scheme 3.60), furnished the diethyl cinnamide ***Z*-3.271** which underwent intramolecular cyclization to naphthol **3.272** in high yield (91%). Finally (point c), with the ACD ring system in hand, the DreM reaction has been attempted on C_1-substitued *O*-carbamoyl naphthalenes **3.274** and **3.278** with disappointing results. While the former undergoes debromination along with the desired carbamoyl migration (**3.275**), the latter suffers cleavage of the carbamoyl group (**3.279**). The aminated carbamoyl naphthalene **3.288** is now being synthesized as an alternative substrate for this DreM reaction.

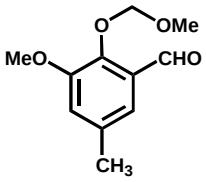
3.6. Experimental Section

General Methods

Please refer to section 2.7.

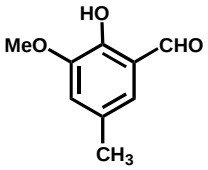
Specific Experimental Procedures

3-Methoxy-2-methoxymethoxy-5-methylbenzaldehyde (3.126)



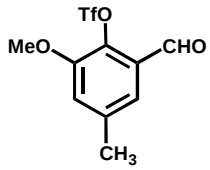
A solution of ^{n}BuLi (1.53 mL, 3.29 mmol, 2.37 M in hexanes) was added dropwise to a stired solution of **3.125**[105] (0.5 g, 2.74 mmol) and TMEDA (0.5 mL, 3.29 mmol) in anhydrous hexanes (5 mL) at 0 °C. The resulting yellow suspension was stirred at 0 °C for 45 min and anhydrous DMF (3.29 mmol, 0.25 mL) was then added while maintaining this temperature. The reaction mixture was allowed to warm up to rt, stirred for an additional 30 min and quenched with a saturated aqueous NH_4Cl solution. Standard work-up and chromatography (hexanes/EtOAc 9:1) yielded 0.50 g of **3.126** (87%) as a yellow oil, IR (film) ν_{max} 1692, 1488, 1329, 1278, 1161, 1071, 949 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.19 (dd, 1H, J = 2.0 and 0.8 Hz), 6.94 (d, 1H, J = 1.6 Hz), 5.15 (s, 2H), 3.83 (s, 3H), 3.52 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 152.2, 147.3, 134.5, 130.0, 119.0, 118.9, 99.54, 57.9, 56.1, 21.2; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 210 (24), 209 (17), 179 (27), 164 (100), 136 (50); HRMS calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0935.

2-Hydroxy-3-methoxy-5-methylbenzaldehyde (3.127)



To a stirred solution of **3.126** (1 g, 4.76 mmol) in methanol (5 mL) at rt was added as aqueous solution of HCl (2.4 mL, 2M). After stirring for 12 h at this temperature, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and concentrated *in vacuo*. The residue was then dissolved in EtOAc and purified through a short silica plug (hexanes:EtOAc 6:4). Recrystallization of the solid obtained from evaporation of the eluate yielded 0.63 g (80%) of **3.127** as yellow needles, mp 72-73 °C (hexanes); IR (KBr) ν_{max} 1649, 1472, 1391, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.86 (1H, s), 9.80 (1H, s), 6.89 (2H, m), 3.85 (3H, s), 2.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 149.5, 147.9, 129.2, 124.0, 120.4, 119.3, 56.2, 20.8; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 167 (57), 166 (100), 165 (24), 120 (10), 91 (10); HRMS calcd for $C_9H_{10}O_3$ 166.0630, found 166.0633.

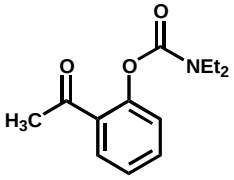
2-Formyl-6-methoxy-4-methylphenyl trifluoromethanesulfonate (3.116)



A flame-dried 500 mL flask was charged with **3.127** (24.80 g, 0.149 mol) and anhydrous CH_2Cl_2 (250 mL). To this stirred solution cooled to 0 °C, NEt_3 (62.4 mL, 0.448 mol) and Tf_2O (30.2 mL, 0.179 mol) were sequentially added. The reaction mixture was stirred for 15 min at 0 °C and quenched by pouring it onto a mixture of crushed ice and brine. Standard work-up and recrystallization of the crude residue yielded 34.2 g (77%) of **3.116** as colourless crystals, mp 57-58 °C (hexanes); IR (KBr) ν_{max} 1713, 1597, 1482, 1423, 1325, 1205, 1134 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.14 (1H, s), 7.26 (1H, dd, J = 2.0 and 0.8 Hz), 7.10 (1H, d, J = 1.6 Hz), 3.91 (3H, s), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 154.4,

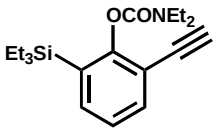
140.1, 137.2, 129.1, 121.8, 119.5, 118.8 (q, J_{CF} = 319 Hz), 56.5, 21.4; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 298 (26), 165 (100), 122 (20), 107 (19); HRMS calcd for $C_{10}H_9F_3O_5S$ 298.0123, found 298.0131.

2-Acetylphenyl diethylcarbamate (3.129)



A 1 L flame-dried flask was charged with NaH (16.16 g, 0.404 mol, 60% dispersion in mineral oil) and dry DMF (450 mL). To this stirred suspension cooled to 0 °C, neat **3.128** (50 g, 0.367 mol) was slowly added while allowing the escape of H_2 through a vent. The reaction mixture was then allowed to warm up to rt and stirred for 3 h or until gas evolution completely ceased. Freshly distilled diethyl carbamoylchloride (51.1 mL, 443.7 mol) was added and the reaction mixture was stirred at rt for 8 h. After removing most of the solvent *in vacuo*, the oily residue was transferred into a separatory funnel containing water (200 mL) and the product was extracted with Et_2O (100 mL x 3). The combined ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue obtained was then distilled bulb to bulb (95 °C/0.1 mmHg) to yield 73.0 g of **3.129** (85%) as clear oil, IR (film) ν_{max} 2977, 1721, 1690, 1603, 1419, 1274, 1206, 1154, 961, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, 1H, *J* = 8 and 1.6 Hz), 7.49 (dt, 1H, *J* = 8 and 1.6 Hz), 7.26 (dt, 1H, *J* = 7.6 and 0.8 Hz), 7.12 (dd, 1H, *J* = 8 and 0.8 Hz), 3.49 (q, 2H, *J* = 7.2 Hz), 3.38 (q, 2H, *J* = 7.2 Hz), 2.55 (s, 3H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.21 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 153.7, 149.8, 133.0, 132.0, 129.6, 125.3, 123.8, 42.3, 42.0, 29.7, 29.6, 14.2, 13.3; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 163 (8), 146 (43), 121 (27), 100 (100), 72 (100); HRMS calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1199.

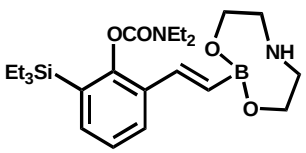
2-Ethynyl-6-(triethylsilyl)phenyl diethylcarbamate (**3.134)**



A solution of **3.129 (**2.75 mL, 12.7 mmol) in anhydrous THF (15 mL) was slowly added to a stirred solution of LDA (18.1 mL, 12.7 mmol, 0.7 M in THF) at –78 °C. The suspension obtained was stirred for 90 min at this temperature and diethyl chlorophosphate (2.0 mL, 13.97 mmol) was added at –78 °C. The reaction mixture was allowed to warm to 0 °C over 5 h and was aged at this temperature and under argon for 10 h. The yellow solution obtained was slowly cannulated into a stirred solution of LDA (38.1 mL, 26.7 mmol, 0.7 M in THF) at –78 °C and the reaction mixture was allowed to warm to 0 °C over the period of 3 h. After lowering the temperature to –78 °C, TMSCl (1.5 mL, 11.8 mmol) was added dropwise and the stirred reaction mixture was allowed to warm to 0 °C. Once again, the temperature was lowered to –78 °C and TESCl (2.55 ml, 15.24 mmol) and a solution of LDA (21.8 mL, 15.24 mmol, 0.7 M in THF) were added under constant stirring. The temperature was allowed to rise to 0 °C and the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. After evaporating most of the THF *in vacuo*, the crude product was extracted with EtOAc and the organic layer was subjected to standard work-up. The resulting crude product was dissolved in MeOH (300 mL) and anhydrous K_2CO_3 (1.75 g, 12.7 mmol) was added. After stirring the reaction mixture for 30 min at rt, the solvent was removed *in vacuo* and the residue was subjected to standard work-up and chromatography (hexanes/EtOAc 9.3/0.7 as eluent) to give 3.70 g (88%) of **3.134** as a clear oil, IR (film) ν_{max} 2114, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, 1H, J = 7.6 and 1.6 Hz), 7.43 (dd, 1H, J = 7.2 and 1.6 Hz), 7.16 (t, 1H, J = 7.6 Hz), 3.27-3.70 (bm, 4H), 3.18 (s, 1H), 1.30 (t, 3H, J = 7.2 Hz), 1.21 (t, 3H, J = 7.2 Hz), 0.95 (t, 9H, J = 8.0 Hz), 0.77-0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 153.3, 136.4, 134.6,

130.4, 124.7, 116.7, 81.5, 79.8, 42.0, 41.8, 14.1, 13.2, 7.4, 3.4; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 303 (47), 302 (100), 145 (16), 100 (100), 72 (62); HRMS calcd for $C_{17}H_{24}NO_2Si$ 302.1576 $[M\text{-}Et]^+$, found 302.1570.

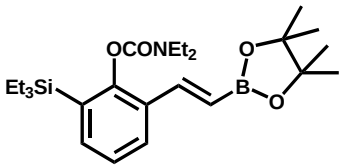
(*E*)-2-(2-(1,3,6,2-Dioxazaborocan-2-yl)vinyl)-6-(triethylsilyl)phenyl diethylcarbamate (3.135)



A flame-dried flask was charged with $NaBH_4$ (4.20 g, 0.111 mol), 2,5-dimethyl-2,4- hexadiene (34.8 mL, 0.244 mol) and anhydrous diglyme (180 mL) and this stirred mixture was cooled in an ice bath. Dimethyl sulphate (10.50 mL, 0.111 mol) was added to this mixture while maintaining the temperature below 5 °C. At the end of the gas evolution that accompanied this addition, the mixture was stirred for 3 h at 0 °C to give a thick suspension to which a sol of **3.134** (33.47 g, 0.101 mol) in dry diglyme (20 mL) was added while maintaining the temperature below 5 °C. This mixture was stirred for 1 h at 0 °C, slowly quenched with H_2O (15 mL) (additional gas evolution resulted), stirred for 30 min at rt, and then treated with formaldehyde (8.3 ml, 0.111 mol, 37 wt % aqueous solution) in a single addition. The resulting exothermic reaction was compensated by application of a rt bath. The reaction mixture was stirred for 24 h at rt and then diluted with EtOAc (200 mL). After separation of the layers, the organic phase was dried (Na_2SO_4) and transferred into a flask containing diethanolamine (11.68, 0.111 mol). The resulting mixture was briefly stirred and concentrated *in vacuo* to 200 mL and, upon standing at 5 °C for 8 h, yielded a colourless solid that was subjected to filtration, washed with EtOAc and recrystallized from EtOH/EtOAc. The first two crops yielded 31.5 g (70%) of **3.135** as colourless crystals, mp 239-240 °C (EtOH/EtOAc); IR (KBr) ν_{max}

1714, 1622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 7.0 Hz), 7.28 (1H, d, J = 7.0 Hz), 7.14 (1H, t, J = 7.3 Hz), 6.90 (1H, d, J = 17.9 Hz), 6.26 (1H, d, J = 17.9 Hz), 5.7 (1H, bs), 3.65-4.0 (5H, m), 3.25-3.55 (2H, m), 2.95-3.1 (3H, m), 2.43-2.6 (2H, m), 1.33 (3H, t, J = 7.1 Hz), 1.13 (3H, t, J = 7.1 Hz), 0.85-0.95 (9H, m), 0.7-9.85 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 153.8, 134.7, 132.5, 131.8, 130.1, 127.2, 125.4, 63.5, 63.2, 51.3, 51.0, 41.8, 41.7, 14.4, 13.3, 7.7, 3.8; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 305 (23), 304 (100), 100 (72), 72 (25); HRMS calcd for $C_{21}H_{34}BN_2O_4Si$ $[M\text{-}Et]^+$ 417.2381, found 417.2367.

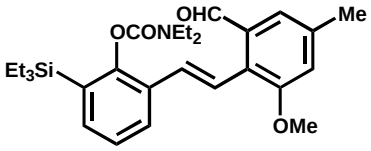
(*E*)-2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-6-(triethylsilyl)phenyl diethylcarbamate (3.114)



Compound **3.135** (8.1 g, 18 mmol) was dissolved in a mixture of H_2O (50 mL) and MeOH (300 mL) and the resulting solution was acidified under stirring with an aqueous solution of HCl (~ 15 mL, 40 mmol, 10 w/v %) to pH 5. Pinacol (3.22 g, 27 mmol) and a 3:1 mixture of hexanes/EtOAc (300 mL) were added and this mixture was stirred overnight. The organic layer was separated, washed with brine, dried with Na_2SO_4 and concentrated *in vacuo* to yield 8.1 g of **3.114** as a colourless solid (98% yield), mp 90-92 °C (hexanes); IR (KBr) ν_{max} 1728, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 8.1 Hz), 7.37-7.43 (2H, m), 7.19 (1H, t, J = 7.4 Hz), 6.11 (1H, d, J = 18.2 Hz), 3.64-3.78 (1H, bs), 3.32-3.45 (3H, m), 1.34 (3H, t, J = 7.6 Hz) 1.17-1.30 (15H, m), 0.94 (9H, t, J = 7.6 Hz), 0.65-0.77 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 153.9, 143.8, 136.4, 130.7, 130.2, 127.7, 125.3, 83.1, 41.7, 41.5, 24.9, 14.2, 13.2,

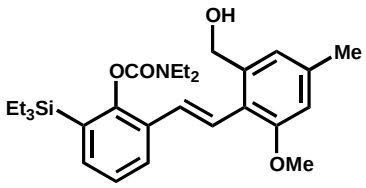
7.4, 3.5; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 431 (30), 430 (100), 429 (22), 100 (57), 72 (23); HRMS calcd for $C_{23}H_{37}BNO_4Si$ $[M\text{-}Et]^+$ 430.2585, found 430.2593.

(*E*)-2-(2-Formyl-6-methoxy-4-methylstyryl)-6-(triethylsilyl)phenyl diethylcarbamate (3.136)



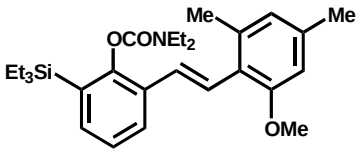
A 500 mL round bottom flask under an argon atmosphere was charged with **3.114** (24.77 g, 54 mmol), **3.116** (20.92 g, 70 mmol), $Pd(PPh_3)_4$ (625 mg, 0.54 mmol) and filled with argon. Degassed DME (200 mL) and a degassed aqueous solution of Na_2CO_3 (135 mL, 0.27 mol, 2M) were sequentially added and the resulting mixture was stirred for 4 h at gentle reflux. Standard work-up and passage of the residue through a short silica plug (hexanes/EtOAc 9:1 as eluent) gave a yellow solid which, upon recrystallization from hexanes, yielded 22.1 g (85%) of **3.136** as yellow needles, mp 124-125 °C (hexanes); IR (KBr) ν_{max} 1712, 1683, 1602 cm^{-1}; ^1H NMR (400 MHz, Acetone-d_6) δ 10.18 (s, 1H), 7.88 (dd, 1H, J = 8.0 and 1.6 Hz), 7.56 (d, 1H, J = 16.4 Hz), 7.44 (dd, 1H, J = 7.2 and 1.6 Hz), 7.28-7.34 (m, 2H), 7.16 (s, 1H), 6.65 (d, 1H, J = 16.4 Hz), 3.94 (s, 3H), 3.35-3.75 (bm, 3H), 3.12-3.23 (bm, 1H), 2.42 (s, 3H), 1.20 (t, 3H, J = 7.2 Hz), 1.12 (t, 3H, J = 7.2 Hz), 0.8-1.0 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 157.9, 154.1, 153.8, 138.4, 135.9, 135.6, 132.2, 130.4, 130.2, 128.9, 127.5, 125.4, 121.3, 120.6, 115.7, 55.9, 41.9, 41.5, 21.6, 14.2, 12.9, 7.4, 3.6; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 481 (M^+, 22), 453 (33), 452 (99), 409 (1), 381 (5), 364 (28), 335 (18), 100 (100), 72 (54); HRMS calcd for $C_{28}H_{39}NO_4Si$ 481.2648, found 481.2647.

(*E*)-2-(2-(Hydroxymethyl)-6-methoxy-4-methylstyryl)-6-(triethylsilyl)phenyl diethylcarbamate (3.137)



A stirred solution of compound **3.136** (11 g, 22.9 mmol) in MeOH (70 mL) was cooled to 0 °C and $NaBH_4$ (0.43 g, 11.5 mmol) was added in portions. After stirring for 2 h the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and the whole was evaporated *in vacuo*. Look for stirring or stirred The residue was extracted with a mixture of water (100 ml) and EtOAc (75 mL x 3) and the organic layer was dried (Na_2SO_4) and concentrated. Recrystallization of the solid obtained yielded 10.3 g of **3.137** (93%) as colourless crystals, mp 98-100 °C (hexanes); IR (KBr) ν_{max} 3420, 1710, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, dd, J = 7.6 and 1.2 Hz), 7.36 (1H, dd, J = 7.6 and 1.6 Hz), 7.25 (t, 1H, J = 7.6 Hz), 7.22 (d, 1H, J = 16.4 Hz), 6.95 (d, 1H, J = 16.4z), 6.91 (s, 1H), 6.69 (s, 1H), 4.73 (d, 2H, J = 6.0), 3.84 (3H, s), 3.58-3.72 (bm, 2H), 3.30-3.43 (bm, 1H), 3.08-3.19 (bm, 1H), 2.37 (s, 3H), 2.15 (t, 1H, J = 6.0 Hz), 1.25 (3H, t, J = 7.2 Hz), 1.15 (3H, t, J = 7.2 Hz), 0.93–0.98 (9H, m), 0.78-0.86 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 154.4, 154.1, 140.3, 138.4, 135.5, 131.7, 130.2, 128.1, 127.9, 125.7, 124.4, 123.4, 122.4, 111.5, 63.8, 55.9, 42.1, 41.8, 22.0, 14.4, 13.3, 7.7, 3.8; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 483 (7), 466 (16), 454 (61);411 (46), 383 (39), 100 (100), 72 (72); HRMS calcd for $C_{28}H_{41}NO_4Si$ 483.2805, found 483.2799.

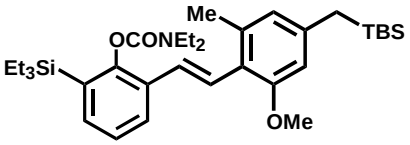
(*E*)-2-(2-Methoxy-4,6-dimethylstyryl)-6-(triethylsilyl)phenyl diethylcarbamate (3.113)



To a stirred solution of **3.137** (7.48 g, 15.5 mmol) and Et^iPr_2N (9.0 mL, 51.1 mmol) in CH_2Cl_2 (75 mL) at –10 °C was added CF_3SO_2Cl (1.44 mL, 18.6 mmol). After 5 min, the reaction mixture was cannulated into ice-cold brine and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1 x 50 mL) and the combined organic layers were evaporated. The oily residue obtained was dissolved in dry DMF (75 mL) and $NaBH_4$ (1.4 g, 37.2 mmol) was added in portions at rt. The reaction mixture was stirred for 9 h and the reaction was quenched with a saturated aqueous NH_4Cl solution. The solvent was evaporated *in vacuo* and the residue was shaken in a water/ether mixture (3:1, 100 mL). The organic layer was washed with H_2O (25 mL), then with brine (25 mL) and dried (Na_2SO_4). Evaporation *in vacuo* gave a solid which, upon recrystallization, yielded 6.8 g of **3.113** (94%) as colourless crystals, mp 109-113 °C (hexanes); IR (KBr) ν_{max} 1729, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (1H, dd, J = 8.0 and 1.6 Hz), 7.33 (1H, dd, J = 7.2 and 1.6 Hz), 7.21 (t, 1H, J = 7.2 Hz), 7.018 (d, 1H, 16.8 Hz), 6.61 (1H, d, J = 16.8 Hz), 6.65 (1H, s), 6.57 (1H, s), 3.81 (3H, s), 3.3-3.7 (3H, m), 3.12-3.25 (1H, m), 2.39 (3H, s), 2.31 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 1.14 (3H, t, J = 7.2 Hz) 0.9-1.0 (9H, m), 0.77-0.86 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 154.2, 137.9, 137.8, 135.2, 132.1, 130.3, 127.6, 127.1, 125.7, 125.1, 124.3, 123.2, 109.8, 55.8, 42.0, 41.8, 21.9, 21.5, 14.6, 13.4, 7.8, 3.8; LRMS (EI, 70 eV) *m/z* (rel. Intensity %) 467 (7), 438 (100), 100 (45), 72 (19); HRMS calcd for $C_{28}H_{41}NO_3Si$ 467.2856, found 467.2855.

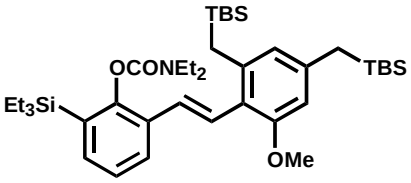
(*E*)-2-(4-((Tert-butyldimethylsilyl)methyl)-2-methoxy-6-methylstyryl)-6-(triethylsi-lyl) phenyl diethylcarbamate (3.140), (*E*)-2-(2,4-Bis((tert-butyldimethylsilyl)methyl)-6-methoxystyryl)-6-(triethylsilyl)-phenyl diethyl-carbamate (3.141) and (*E*)-2-(2-((Tert-butyldimethylsilyl)methyl)-6-methoxy-4-methylstyryl)-6-(triethylsilyl)phenyl diethyl carbamate (3.142)

A 50 mL flame-dried flask was charged with **3.113** (1.0 g, 2.14 mmol), TBSCl (0.645 g, 4.28 mmol) and dry THF (10 mL). After cooling the resulting solution to –30 °C, a solution of LDA (6.11 mL, 2.14 mmol, 0.7 M in THF) was added dropwise under constant stirring and the temperature was allowed to rise to 23 °C over 1.5 h. After stirring for ~ 30 min, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and was subjected to standard work-up. Chromatography (hexanes/EtOAc 9.65/0.35) of the crude oil gave sequentially 0.48 g of **3.141** (32%), 0.30 g of **3.140** (24%), 80 mg of **3.142** (6%) and 0.31 g of **3.113** (31%) as clear oils.



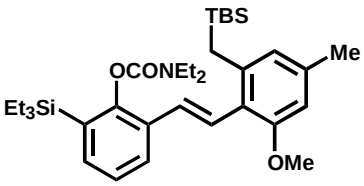
3.140

IR ν_{max} 1724, 1623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, 1H, J = 7.6 and 1.2 Hz), 7.33 (dd, 1H, J = 7.2 and 1.6 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.18 (d, 1H, J = 16.4 Hz), 7.05 (d, 1H, J = 16.4 Hz), 6.49 (s, 1H), 6.41 (s, 1H), 3.80 (s, 3H), 3.37-3.72 (bm, 3H), 3.15-3.26 (bm, 1H), 2.38 (s, 3H), 2.05 (s, 2H), 1.27 (t, 3H, J = 6.8 Hz), 1.13 (t, 3H, J = 7.2 Hz), 0.78-0.97 (m, 24H), -0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 153.9, 140.5, 137.4, 134.7, 132.0, 129.9, 127.3, 126.2, 125.5, 124.9, 123.4, 121.4, 108.9, 55.5, 41.7, 41.5, 26.6, 22.8, 21.3, 16.8, 14.2, 13.1, 7.5, 3.5, -6.2; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 581 (12), 552 (100), 524 (33), 509 (27), 481 (23), 100 (51), 72 (37); HRMS calcd for $C_{34}H_{55}NO_3Si_2$ 581.3720, found 581.3727.



3.141

A higher yield of this compound can be obtained by using an excess of TBSCl and LDA. Thus, in a 25 mL flame-dried flask, **3.113** (0.3 g, 0.64 mmol) and TBSCl (0.48 g, 3.21 mmol) were dissolved in dry THF (6 mL). After cooling this solution to –30 °C, a solution of LDA (4.6 mL, 3.21 mmol, 0.7 M in THF) was added dropwise and the reaction mixture was allowed to warm to 23 °C. After stirring for 3 h, the reaction was quenched with a saturated aqueous NH_4Cl solution and the crude mixture was subjected to standard work-up. Chromatography (hexanes/EtOAc 9.65/0.35) of the crude material yielded 270 mg of **3.141** (60%) as clear oil, IR ν_{max} 1728, 1626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, 1H, J = 7.2 and 1.6 Hz), 7.31 (dd, 1H, J = 7.2 and 1.6 Hz), 7.23 (d, 1H, J = 16.0 Hz), 7.19 (t, 1H, 7.6 Hz), 6.99 (d, 1H, J = 16.0 Hz), 6.32 (s, 1H), 6.31 (s, 1H), 3.78 (s, 3H), 3.34-3.70 (bm, 3H), 3.17-3.29 (bm, 1H), 2.21 (d, 2H, J = 5.6 Hz), 2.03 (s, 2H), 1.28 (t, 3H, J = 7.2 Hz), 1.13 (t, 3H, J = 7.2 Hz) 0.77-0.99 (m, 33H), -0.06 (s, 6H), -0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 153.9, 141.2, 140.1, 134.5, 132.3, 129.9, 126.8, 126.0, 125.5, 125.3, 122.3, 120.0, 107.7; 55.3, 41.6, 41.4, 26.5, 22.9, 20.1, 16.9, 14.2, 13.1, 7.8, 3.8, 5.8, -6.3; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 666 (100), 638 (62), 623 (56), 595 (65), 431 (33), 100 (50), 72 (41); HRMS calcd for $C_{40}H_{69}NO_3Si_3$ 695.4585, found 695.4591.



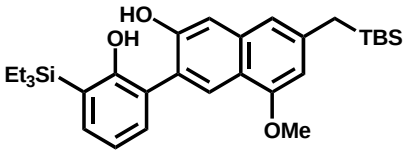
3.142

IR ν_{max} 1726, 1626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, 1H, J = 8.0 and 1.6 Hz), 7.31 (dd, 1H, J = 8.0 and 1.6 Hz), 7.22 (d, 1H, J = 16.4 Hz), 7.19 (t, 1H, J = 6.0 Hz), 6.98 (d, 1H, J = 16.0 Hz), 6.47 (s, 2H), 3.78 (s, 3H), 3.34-3.69 (bm, 3H), 3.12-3.24 (bm, 1H), 2.29 (s, 3H), 2.23 (m, 2H), 1.27 (t, 3H, J = 7.2 Hz),

1.13 (t, 3H, J = 7.2 Hz) 0.88-0.97 (m, 18H), 0.77-0.85 (m, 6H), -0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 153.9, 141.2, 137.0, 134.6, 132.1, 130.0, 126.8, 126.5, 125.3, 123.0, 121.3, 108.1, 55.3, 41.7, 41.4, 26.5, 21.6, 20.0, 16.9, 14.2, 13.1, 7.5, 3.5, -5.8; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 581 (8), 552 (100), 524 (41), 509 (32), 481 (20), 100 (63), 72 (44); HRMS calcd for $C_{34}H_{55}NO_3Si_2$ 581.3720, found 581.3725.

Desilylation of 3.141 A flame-dried 2 mL flask was charged with **3.141** (50 mg, 0.072 mmol) and THF (1 mL). To this stirred solution at 0 °C was added TBAF (0.144 mL, 0.144 mmol) and the resulting reaction mixture was stirred for 4h at rt. Standard work up and chromatography of the crude residue (8.5:1.5 hexanes/EtOAc) gave 30 mg of **3.113** (88%).

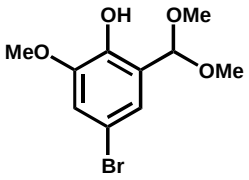
7-(Tert-butyldimethylsilyl)methyl)-3-(2-hydroxy-3-(triethylsilyl)phenyl)-5-methoxynaphthalen-2-ol (3.143)



A solution of LDA (2.22 mL, 1.5 mmol, 0.7 M in THF) was added dropwise to a stirred solution of **3.140** (0.283 g, 0.48 mmol) in THF (5 mL) at –7 °C. The reaction mixture was allowed to warm to rt and, after stirring for 3h, the conversion of **3.140** was judged complete (TLC, hexanes/EtOAc 8.5:1.5). Work-up and chromatography (hexanes/EtOAc 9.8:0.2 as eluent) gave 73 mg (30%) of **3.143** as clear oil, IR (film) ν_{max} cm^{-1} 3300, 2954, 2874, 1634, 1571, 1459, 1417, 1390, 1248, 1164, 1004, 908, 851, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.45 (dd, 1H, J = 7.2 and 1.6 Hz), 7.31 (dd, 1H, J = 7.2 and 1.6 Hz), 7.23 (s, 1H), 7.05 (t, 1H, J = 7.2 Hz), 6.95 (s, 1H), 6.4 (s, 1H), 5.42 (s, 1H), 5.15 (bs, 1H), 3.95 (s, 3H), 2.24 (s, 2H), 0.73-1.01 (m, 24H), -0.05 ppm (s,

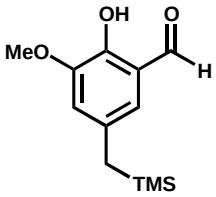
6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ158.5, 155.2, 151.7, 140.5, 136.8, 136.4, 132.3, 125.2, 124.1, 122.6, 122.1, 120.9, 118.9, 116.6, 109.9, 104.8, 55.4, 26.6, 23.7, 16.9, 7.7, 3.6, -6.2; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 509 (23), 477 (29), 464 (30), 385 (48), 363 (60), 245 (48), 219 (38), 183 (40); HRMS calcd for $C_{30}H_{44}O_3Si_2$ 508.2829, found 508.2833.

4-Bromo-2-(dimethoxymethyl)-6-methoxyphenol (3.146)



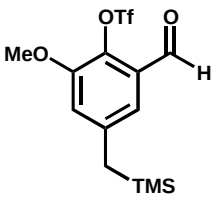
A 500 mL flask was charged with **3.145**[106] (16 g, 69 mmol) and PTSA·H_2O, (0.656 g, 3.45 mmol) and anhydrous MeOH (160 mL) was added. To this solution at rt was added, under constant stirring, $CH(OMe)_3$ (53 mL, 0.483 mol) and the resulting dark red solution was refluxed for 16 h. The reaction mixture was allowed to warm to rt and quenched by the addition of solid Na_2CO_3 (1.28 g; 10.3 mmol). Methanol was removed *in vacuo* and the residue was redissolved in EtOAc (100 mL). The organic layer was sequentially washed with a 10% aqueous solution of Na_2CO_3 (2 x 100 mL) and with a 9:1 mixture of brine/10% aqueous solution of Na_2CO_3 (1 x 100 mL). The resulting organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallization of the resulting residue (hexanes/EtOAc) yielded 11.56 g of **3.146** (61%) as light brown crystals, mp 144-146; IR (KBr) ν_{max} 3297; ^{1}H NMR (400 MHz, MeOD) δ 7.12 (s, 1H), 7.05 (s, 1H), 5.62 (s, 1H), 3.87 (s, 3H), 3.36 (s, 6H); ^{13}C NMR (100 MHz, MeOD) δ 148.4, 143.8, 125.7, 121.4, 114.2, 110.0, 99.3, 55.4, 52.8; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 278 (2), 276 (2), 263 (8), 261 (7), 247 (16), 245 (16), 165 (44), 89 (56); HRMS calcd for $C_{10}H_{13}BrO_4$ 275.9997, found 275.9990.

2-Hydroxy-3-methoxy-5-((trimethylsilyl)methyl)benzaldehyde (3.148)



A 100 mL flask was charged with **3.146** (1 g, 3.61 mmol), POPd2 (24.5 mg, 0.036 mmol) and anhydrous THF (20 mL). To this stirred mixture to –78 °C, a solution of ^{n}BuLi (1.4 mL, 3.25 mmol, 2.32 M in hexanes) and a solution of $TMSCH_2MgCl$ (7.6 mL; 7.58 mmol, 1M in diethyl ether) were sequentially added and the reaction mixture was allowed to warm to rt. After stirring for 12 h the resulting dark brown solution was cannulated into an ice-cold saturated aqueous NH_4Cl solution. The oily residue obtained from standard work-up of the crude mixture was dissolved in CH_2Cl_2 (20 mL) and the solution was transferred to a flask containing a mixture of silica gel (1 g) and oxalic acid (0.3 mL of 10% aqueous sol.). After stirring for 16 h at rt, the reaction mixture was subjected to filtration and the eluate was concentrated to dryness to yield 0.82 g of **3.148** (96%) as yellow oil, IR (film) ν_{max} 2954, 2895, 2843, 1656, 1467, 1265 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.80 (s, 1H), 9.83 (s, 1H), 6.76 (s, 2H), 3.87 (s, 3H), 2.04 (s, 2H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 148.3, 147.7, 131.9, 122.5, 120.4, 118.5, 56.1, 26.0, -2.1; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 238 (36), 223 (18), 222 (22), 207 (46), 73 (100); HRMS calcd for $C_{12}H_{18}O_3Si$ 238.1025, found 238.1031.

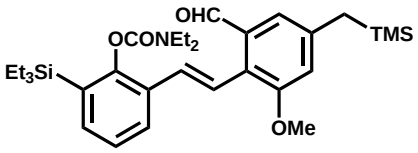
2-Formyl-6-methoxy-4-((trimethylsilyl)methyl)phenyl trifluoromethanesulfonate (3.149)



A stirred solution of **3.148** (10.37 g, 43.6 mol) and Et_3N (18.2 mL; 130.7 mol) in anhydrous CH_2Cl_2 (100 mL) was cooled to 0 °C and Tf_2O (8.8 mL, 52.3 mol) was added dropwise. After stirring for 5 min at this temperature, the reaction mixture was cannulated into an ice-cold saturated

aqueous NH_4Cl solution. Standard work-up and passage through a silica plug (hexane:EtOAc 9:1 as eluent) gave 13.55 g of **3.149** (84%) which was sufficiently pure for the following reaction. Recrystallization of the solid furnished **3.149** (61% from 1st crop) as colourless crystals, mp 57-58 °C (hexanes); IR (KBr) ν_{max} 2951, 2738, 1702, 1323, 1136 cm_{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.14 (d, 1H, J = 1.5 Hz), 6.91 (d, 1H, J = 1.5 Hz), 3.94 (s, 3H), 2.19 (s, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.0, 151.2, 143.1, 136.3, 129.0, 120.0, 118.3 (q, J_{CF} = 320 Hz), 56.4, 27.5, -2.0; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 370 (2), 355 (8), 237 (100), 222 (12), 136 (22), 73 (100); HRMS calcd for $C_{13}H_{17}F_3O_5SSi$ 370.0518, found 370.0524.

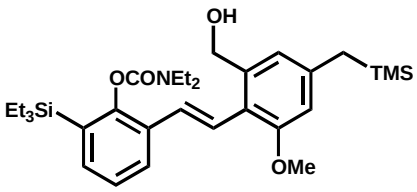
(*E*)-2-(2-Formyl-6-methoxy-4-((trimethylsilyl)methyl)styryl)-6-(triethylsilyl)phenyl diethylcarbamate (3.150)



A 500 mL flask charged with **3.149** (7.66 g; 20.7 mmol), **3.114** (7.32 g; 15.9 mmol) and $Pd(PPh_3)_4$ (0.239 g; 0.207 mmol) was fitted with a condenser and the system was flushed with argon. A degassed aqueous of Na_2CO_3 (51.8 mL, 0.104 mol, 2M) and degassed DME (100 mL) were sequentially added and the reaction mixture was stirred at reflux for 4h. Standard work-up, chromatography (hexanes:EtOAc 9:1) and recrystallization yielded 6.6 g **3.150** (75%) as yellow solid, mp 93-94 °C (hexanes); IR (KBr) ν_{max} 1718, 1678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.85 (dd, 1H, J = 8.0 and 1.0 Hz), 7.49 (d, 1H, J = 16.5 Hz), 7.42 (dd, 1H, J = 7.5 and 1.5 Hz), 7.28 (t, 1H, J = 7.5 Hz), 7.20 (d, 1H, J = 1.0 Hz), 6.75 (d, 1H, J = 1.0 Hz), 6.51 (d, 1H, J = 16.5 Hz), 3.89 (s, 3H), 3.62-3.73 (m, 2H), 3.35-3.46 (m, 1H), 3.18-3.28 (m, 1H), 2.19 (s, 2H),

1.23 (t, 3H, J = 7.0 Hz), 1.15 (t, 3H, J = 7.0 Hz), 0.99 (t, 9H, J = 8.0 Hz), 0.84 (m, 6H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 158.2, 154.5, 154.2, 141.9, 136.2, 136.0, 132.2, 130.8, 127.9, 125.8, 121.9, 119.9, 115.2, 56.2, 42.2, 41.9, 27.9, 14.5, 13.3, 7.8, 3.9, -1.4; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 553 (24), 538 (2), 524 (87), 481 (2), 453 (7), 436 (39), 100 (100), 72 (66); HRMS calcd for $C_{31}H_{47}NO_4Si_2$ 553.3044, found 553.3029.

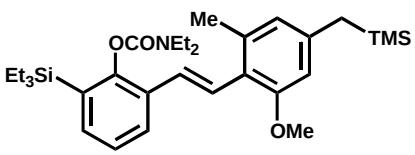
(*E*)-2-(2-(Hydroxymethyl)-6-methoxy-4-((trimethylsilyl)methyl)styryl)-6-(triethylsilyl)phenyl diethylcarbamate (3.151)



$NaBH_4$ (0.20 g, 5.42 mmol) was added in portions to a stirred solution of **3.150** (6.00 g, 10.85 mmol) in MeOH (50 mL) at 0 °C. After stirring for 1h at this temperature, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and the solvent was removed under reduced pressure. The residue was shaken in a mixture of water and EtOAc (1:1, 50 mL) and the organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to yield 5.3 g of **3.151** (63%) as a colourless solid, mp 86-90°C (hexanes); IR (KBr) ν_{max} 3468, 1693, 1161 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, 1H, J = 7.5 and 1.0 Hz), 7.36 (dd, 1H, J = 7.5 and 1.5 Hz), 7.23 (t, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 16.5 Hz), 6.98 (d, 1H, J = 16.5 Hz), 6.73 (s, 1H), 6.52 (s, 1H), 4.72 (bm, 2H), 3.82 (s, 3H), 3.55-3.72 (bm, 2H), 3.36-3.47 (m, 1H), 3.15-3.23 (m, 1H), 2.13 (m, 2H), 2.11 (s, 1H), 1.26 (t, 3H, J = 7.0 Hz), 1.14 (t, 3H, J = 7.0 Hz), 0.97 (t, 9H, J = 8.0 Hz), 0.84 (t, 6H, J = 7.5 Hz), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.1, 153.8, 141.0, 139.8, 135.1, 131.5, 129.8, 127.6, 127.3, 125.4, 124.2, 121.6, 121.3, 110.3, 63.8, 55.6, 41.7, 41.5, 27.5, 14.1,

13.0, 7.4, 3.5, -1.8; MS (EI, 75 eV): *m/z* (rel. intensity %) 555 (M^+, 3), 537 (33), 508 (52), 465 (68), 100 (100), 72 (68); ES HRMS (calcd for $C_{31}H_{49}NO_4Si_2$) 555.3200, found 555.3210.

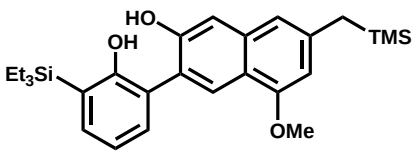
(*E*)-2-(2-Methoxy-6-methyl-4-((trimethylsilyl)methyl)styryl)-6-(triethylsilyl)phenyl diethylcarbamate (3.152)



A solution of **3.151** (2.00 g; 3.60 mmol) and Et^iPr_2N (2.08 mL; 11.9 mmol) in CH_2Cl_2 (20 mL) was cooled to –10 °C and CF_3SO_2Cl (0.280 mL; 4.32 mmol) was added dropwise while stirring. After 5 min, the reaction mixture was cannulated into ice-cold brine and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The clear oily residue thus obtained was dissolved in dry DMF (20 mL) and $NaBH_4$ (0.327 g; 8.64 mmol) was added in portions at rt. The reaction mixture was stirred for 14 h and then quenched with a saturated aqueous NH_4Cl solution. The solvent was evaporated *in vacuo* and the residue was shaken in a mixture of water and ether (3:1, 60 mL). The organic layer was separated, washed with water (25 mL), then with brine (25 mL) and dried over Na_2SO_4. *In vacuo* evaporation of the solvent gave a solid which, upon recrystallization, yielded 1.4 g of **3.152** (72%) as colourless crystals, mp 88-90 °C (hexanes); IR (KBr) ν_{max} cm^{-1} 2953, 2874, 1716, 1602, 1453, 1399, 1308, 1260, 1155, 1078, 964, 852, 732; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, 1H, J = 8.0 and 1.0 Hz), 7.36 (dd, 1H, J = 7.0 and 1.5 Hz), 7.24 (t, 1H, J = 7.5 Hz), 7.22 (d, 1H, J = 16.5 Hz), 7.90 (d, 1H, J = 16.5 Hz), 6.50 (s, 1H), 6.43 (s, 1H), 3.83 (s, 3H), 3.65-3.72 (bm, 1H), 3.40-3.60 (bm, 2H), 3.20-3.30 (bm, 1H), 2.42 (s, 3H), 2.07 (s, 2H), 1.30 (t, 4H, J = 7.5 Hz),

1.69 (t, 3H, J = 7.0 Hz), 0.99 (t, 9H, J = 8.0 Hz), 0.82-0.89 (m, 6H), 0.04 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.9, 153.9, 153.8, 140.3, 137.4, 134.7, 132.0, 129.9, 127.3, 126.2, 125.4, 125.0, 123.1, 121.5, 108.7, 55.5, 41.7, 41.5, 27.3, 21.3, 14.2, 13.1, 7.5, 3.5, -1.8; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 539 (10), 524 (2), 510 (100), 100 (48), 72 (30); HRMS calcd for $C_{31}H_{49}NO_3Si_2$ 539.3251, found 539.3245.

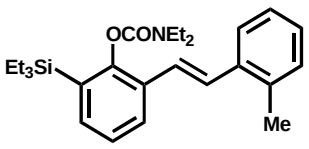
3-(2-Hydroxy-3-(triethylsilyl)phenyl)-5-methoxy-7-((trimethylsilyl)methyl)naphthalen-2-ol (3.153)



A 25 mL flame-dried flask under an Ar atmosphere was charged with **3.152** (0.576 g, 1.07 mmol) and dry THF (5 mL) and the stirred solution was cooled to −10 °C. Upon dropwise addition of a solution of LDA (4.40 mL, 3.30 mmol, 0.75 M) the reaction mixture took on a deep blue colour, although TLC monitoring did not reveal formation of a new product. The reaction mixture was then allowed to warm to rt over 30 min and transferred into a saturated aqueous NH_4Cl solution. Standard work-up yielded a foamy mixture of complex composition whose chromatography (hexanes/EtOAc 9.75:0.25) yielded 75 mg of **3.153** (15%) as clear oil, IR (KBr) ν_{max} cm^{-1} 2954, 2874, 1634, 1571, 1459, 1417, 1390, 1248, 1164, 1004, 851, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.45 (dd, 1H, J = 7.2 and 1.6 Hz), 7.32 (dd, 1H, J = 7.2 and 1.6 Hz), 7.22 (s, 1H), 7.06 (t, 1H, J = 7.2 Hz), 6.93 (s, 1H), 6.39 (d, 1H, J = 1.2 Hz), 3.95 (s, 3H), 2.23 (s, 2H), 0.72-1.02 (m, 15H), 0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 155.5, 152.0, 140.6, 137.1, 136.7, 132.6, 125.5, 124.4, 122.9, 122.4, 121.1, 119.1, 116.6, 110.1, 104.9, 55.6, 28.4, 7.9, 3.8, -1.4; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 467 (M+1, 25),

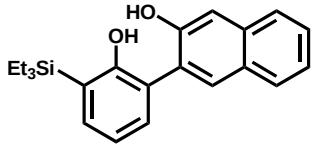
466 (M^+, 100), 437 (23), 363 (18), 73 (29); HRMS calcd for $C_{27}H_{38}O_3Si_2$ 466.2360, found 466.2346.

(*E*)-2-(2-Methylstyryl)-6-(triethylsilyl)phenyl diethylcarbamate (3.168)



A 50 mL flask charged with 2-iodotoluene (0.36 mL, 2.82 mmol), **3.114** (1.00 g, 2.17 mmol) and $Pd(PPh_3)_4$ (33 mg, 0.028 mmol) was fitted with a condenser and the system was flushed with argon. A degassed aqueous solution of Na_2CO_3 (7 mL, 14.1 mmol, 2M) and degassed DME (15 mL) were sequentially added and the reaction mixture was stirred at reflux for 9 h. Standard work-up and passage through a short silica plug (hexanes:EtOAc 9.5:0.5) yielded 0.72 g of **3.168** (78%) as a clear oil, IR (KBr) ν_{max} cm^{-1} 2953, 2874, 1722, 1400, 1271, 1152, 959, 734; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, 1H, J = 7.0 Hz), 7.54 (bm, 1H), 7.42 (d, 1H, J = 7.0 Hz), 7.25-7.34 (m, 2H), 7.20-7.25 (bm, 3H), 7.00 (d, 1H, J = 16.5 Hz), 3.68-3.82 (bm, 1H), 3.32-3.57 (bm, 3H), 2.46 (s, 3H), 1.35 (t, 3H, J = 7.0 Hz), 1.21 (t, 3H, J = 7.0 Hz), 1.02 (t, 9H, J = 8.0 Hz), 0.83-0.95 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 154.6, 154.3, 137.1, 136.3, 135.8, 131.3, 130.8, 130.7, 128.6, 128.1, 127.9, 126.5, 125.8, 125.8, 124.8, 42.3, 42.0, 20.4, 14.8, 13.6, 7.9, 4.0; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 423 (M^+, 18), 395 (90), 394 (100), 294 (9), 237 (18), 219 (28), 191 (21), 189 (12); HRMS (calcd for $C_{26}H_{37}NO_2Si$) 423.2594, found 423.2610.

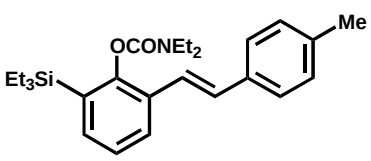
3-(2-Hydroxy-3-(triethylsilyl)phenyl)naphthalen-2-ol (3.169)



A 25 mL flame-dried flask under an Ar atmpshere was charged with **3.168** (0.70 g, 1.65 mmol) and dry THF (5 mL) and the

resulting solution was cooled to −10 °C. Upon dropwise addition of solution of LDA (5.0 mL, 3.46 mmol, 0.7 M) the stirred mixture became yellow, although TLC monitoring did not reveal any product. The reaction mixture was then allowed to warm to rt and, after stirring for 2 h, it was quenched with a saturated aqueous NH_4Cl solution. Standard work-up yielded a foam of complex composition which was subejected to chromatography (hexanes/EtOAc 9.5:0.5) and recrystallization to give 52 mg of **3.169** (9%) as colourless flakes, mp 184-185 °C (hexanes/EtOAc); IR (KBr) ν_{max} cm^{-1} 3320, 2987, 2862, 1643, 1561, 1433, 1369, 1244, 1132, 908, 841, 747; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77-7.80 (m, 2H), 7.74 (d, 1H, J = 8.4 Hz), 7.45-7.49 (m, 2H), 7.40 (s, 1H), 7.37 (t, 1H, J = 7.8 Hz), 7.31 (dd, 1H, J = 7.8 and 1.8 Hz), 7.07 (t, 1H, J = 7.8 Hz), 5.22-5.50 (bs, 1H), 5.29 (s, 1H), 1.00 (t, 9H, J = 7.8 Hz), 5.86-5.95 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.7, 151.4, 137.6, 135.2, 132.5, 131.2, 129.5, 128.2, 127.4, 126.9, 125.8, 124.9, 124.7, 121.8, 121.5, 111.5, 8.1, 4.0; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 350 (M^+, 10), 321 (100), 291 (11), 275 (15), 247 (25), 218 (17), 189 (22); HRMS calcd for $C_{22}H_{26}O_2Si$ 350.1702, found 350.1689.

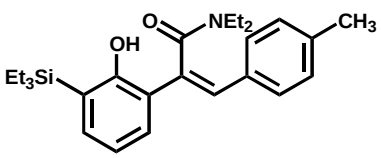
(*E*)-2-(4-Methylstyryl)-6-(triethylsilyl)phenyl diethylcarbamate (3.171)



A 100 mL flask charged with 4-iodotoluene (0.615 g, 3.60 mmol), **3.114** (1.5 g, 3.26 mmol) and $Pd(PPh_3)_4$ (0.188 g, 0.163 mol) was fitted with a condenser and the system was flushed with argon. A degassed aqueous solution of Na_2CO_3 (8.15 mL, 16.3 mmol, 2M) and degassed DME (20 mL) were sequentially added and the reaction mixture was stirred at reflux for 9 h. Standard work-up and chromatography (hexanes:EtOAc 9.5:0.5) yielded 1.19 g of **3.171** (86%) as colourless solid, mp 103-104 °C (hexanes/EtOAc); IR

(KBr) ν_{max} cm^{-1} 2951, 2874, 1706, 1403, 1261, 1201, 1157, 966, 732; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, 1H, J = 8.0 and 1.6 Hz), 7.35-7.39 (m, 3H), 7.24 (t, 1H, J = 7.6 Hz), 7.14-7.20 (m, 2H), 7.04 (s, 2H), 3.67-3.80 (bm, 1H), 3.39-3.52 (bm, 3H), 2.38 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz), 1.21 (t, 3H, J = 7.2 Hz), 0.99 (t, 9H, J = 8.0 Hz), 0.81-0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.9, 137.5, 135.2, 134.9, 130.7, 130.4, 130.2, 129.3, 127.6, 126.4, 125.4, 122.1, 41.9, 41.6, 21.3, 14.4, 13.2, 7.5, 3.6; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 423 (4), 395 (30), 394 (100), 100(61), 72 (25); HRMS calcd for $C_{26}H_{37}NO_2Si$) 423.2594, found 423.2588.

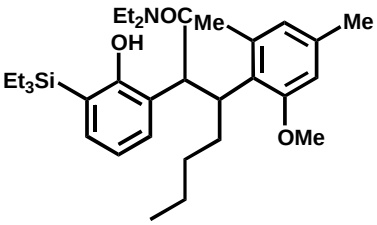
(*Z*)-*N*,*N*-Diethyl-2-(2-hydroxy-3-(triethylsilyl)phenyl)-3-*p*-tolylacrylamide (3.172)



A 50 mL flame-dried flask under with Ar atmosphere was charged with **3.171** (0.79 g, 1.87 mmol) and dry THF (8 mL) and the resulting stirred solution was cooled to −10 °C. Upon addition of a solution LDA (2.93 mL, 2.06 mmol, 0.7 M) the mixture took on a deep blue colour, although TLC monitoring did not reveal formation of any products. The mixture was then allowed to warm to rt and, after stirring for 2 h, quenched with a saturated aqueous NH_4Cl solution. Standard work-up yielded a foam of complex composition which, upon chromatography (hexanes/EtOAc 9.85:0.015) and sequential recrystallization of the purified product, gave 81 mg of **3.172** (10%) as colourless solid, mp 96-97 °C; IR (KBr) ν_{max} cm^{-1} 3468, 2951, 2874, 1580, 1459, 1407, 750, 727; ^1H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.35 (dd, 1H, J = 7.5 and 1.5 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.21 (dd, 1H, 15.0 and 1.5 Hz), 7.16 (d, 2H, J = 7.5 Hz), 6.90 (t, 1H, J = 7.0 Hz), 6.63 (s, 1H), 3.68 (oct, 1H, J = 7.0 Hz), 3.34 (oct, 1H, J = 7.0 Hz), 3.25 (oct, 1H, J =

7.0 Hz), 3.17 (oct, 1H, J = 7.0 Hz), 2.38 (s, 3H), 1.16 (t, 3H, J = 7.0 Hz), 0.99 (t, 9H, J = 8.0 Hz), 0.87-0.94 (m, 6H), 0.80 (t, 3H, J = 7.5 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.7, 161.1, 138.4, 136.4, 134.1, 133.1, 132.6, 130.7, 129.2, 128.2, 124.8, 124.6, 119.1, 43.1, 39.4, 21.3, 13.4, 11.9, 7.7, 3.5; LRMS (EI, 75 eV) *m/z* (rel. intensity %) 423 (M^+, 6), 394 (19), 351 (19), 350 (62), 322 (20), 321 (70), 293 (40), 266 (20), 265 (63), 238 (20), 237 (100), 178 (18); HRMS calcd for $C_{26}H_{37}NO_2Si$ 423.2594, found 423.2588.

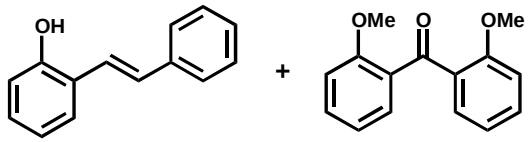
_N_,_N_-Diethyl-2-(2-hydroxy-3-(triethylsilyl)phenyl)-3-(2-methoxy-4,6-dimethylphenyl) heptanamide (3.184a)



A 10 mL flame-dried flask under an Ar atmosphere was charged with **3.113** (0.10 g, 0.22 mmol) and dry THF (5 mL) and the resulting stirred solution was cooled to −78 °C. A solution of ^{n}BuLi (0.20 mL, 0.46 mmol, 2.27 M in hexanes) was added dropwise and the temperature was allowed to rise to 23 °C. After stirring for 20 min, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and the crude material was subjected to standard work-up. The solid obtained was found analytically pure by NMR and was recrystallized from hexanes to give 0.10 g of **3.184a** (87%) as colourless crystals, mp 121-122 °C (hexanes); IR (KBr) ν_{max} cm^{-1} 3470, 2952, 2872, 2731, 2629, 1611, 1282, 1568, 1468, 1427, 1269, 1150, 1112, 1082, 1005, 829, 753, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (bs, 1H), 7.02 (dd, 1H, J = 7.2 and 1.6 Hz), 6.60 (bs, 1H), 6.44 (t, 1H, J = 7.2 Hz), 6.41 (s, 1H), 6.32 (s, 1H), 4.77 (d, 1H, J = 11.2 Hz), 4.04 (dt, 1H, J = 11.2 and 3.2 Hz), 3.87 (s, 3H), 3.48-3.70 (m, 3H), 3.25-3.35 (m, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 1.95-2.05 (bm, 1H), 1.45-1.57 (bm, 1H), 1.37 (t, 3H, J = 6.8 Hz), 1.10-1.30 (m, 6H), 0.76-1.05 (m, 19H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 176.5, 162.7, 157.9, 140.0, 136.2, 135.2, 133.2, 125.4, 125.3, 124.2, 122.8, 118.6, 109.8, 55.1, 50.8, 43.7, 42.2, 40.8, 31.3, 30.7, 23.4, 21.6, 21.1, 15.1, 14.3, 13.1, 8.0, 3.7; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 525 (21), 496 (50), 450 (12), 291 (56), 218 (72), 205 (100), 191 (69) 163 (26), 149 (100), 119 (93); HRMS calcd for $C_{32}H_{51}NO_3Si$ 525.3638, found 525.3641.

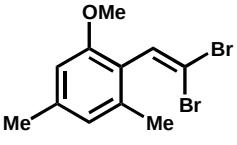
(*E*)-2-Styrylphenol (3.205) and 2,2'-Dimethoxybenzophenone (3.206)



3.205 3.206

A solution of *o*-anisyllithium (**3.204**) was prepared according to a known procedure.[107] Thus, a solution of ^{n}BuLi (0.170 mL, 0.355 mmol, 2.08 M in hexanes) was added to a stirred solution of *o*-bromoanisole (0.044 mL, 0.355 mmol) in anhydrous hexanes (2 mL) at rt. While stirring this mixture for 10 min, a colourless solid appeared. A solution of **3.203** (50 mg, 0.169 mmol) in THF (1.5 mL) was added to this solution of **3.204** and the resulting mixture was stirred for 90 min at rt. The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution and subjected to standard work-up. Chromatography of the crude material (hexanes : EtOAc 8.5:1.5 as eluent) yielded 32 mg of **3.205**[108] (98%) and 14 mg of **3.206**[109] (34%) whose spectral data were found to be consistent with those reported for the known materials.

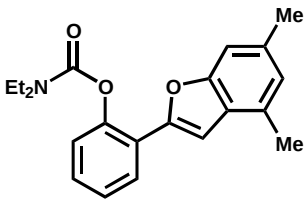
2-(2,2-Dibromovinyl)-1-methoxy-3,5-dimethylbenzene (3.208a)



A 250 mL flask was charged with of **3.218**[72] (3.79 g, 23 mmol) and CBr_4 (11.5, 34.5 mmol). CH_2Cl_2 (100 mL) was added and the resulting stirred solution was cooled to 0 °C. A solution of PPh_3 (18.08 g, 69 mmol) in CH_2Cl_2 (80 mL) was added dropwise from a vented addition

funnel under vigorous stirring (the formation of copious amounts of PPh_3O was observed). After stirring this mixture for 20 min at 0 °C, the solvent was removed under reduced pressure and the residue was suspended in $CHCl_3$ (70 mL). The solid was subjected to filtration and washed with ~ 20 mL of $CHCl_3$. The eluate was concentrated *in vacuo* and the residue was passed rapidly purified through a silica plug (hexanes/EtOAc 9.75/0.25 as eluent). Recrystallization of the crude product (hexanes/EtOAc) afforded 4.82 g of **3.208a** as colourless plates (4.0 g from 1st crop and 0.89 g from 2nd crop, 66%), mp 62-63°C (pentane); IR (KBr) (ν_{max} cm^{-1}) 3002, 2961, 8238, 1605, 1574, 1461, 1318, 1202, 1147, 1094, 872, 836, 756; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 1H), 6.64 (s, 1H), 6.54 (s, 1H), 3.79 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 139.2, 137.1, 134.4, 123.1, 122.2, 109.0, 92.7, 55.6, 21.7, 19.7; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 322 (18), 320 (38), 318 (19), 241 (16), 239 (17), 226 (38), 224 (38), 160 (100), 145 (49), 115 (43); HRMS calcd for $C_{11}H_{12}Br_2O$ 317.9255, found 317.9248.

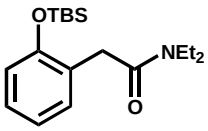
2-(4,6-Dimethylbenzofuran-2-yl)phenyl diethylcarbamate (3.220)



A 50 mL flask was charged with **3.208a** (0.30 g, 0.94 mmol), **3.207c** (0.26 g, 0.98 mmol), $P(2\text{-fur})_3$ (32.6 mg, 140 mmol), $Pd_2(dba)_3$ (21.4 mg, 23.4 mmol) and fitted with a condenser. After flushing the system with Ar, TBAF (0.094 mmol, 0.10 mL, 1M in THF), a degassed aqueous Na_2CO_3 solution (1.40 mL, 2.81 mmol, 2M), and toluene (10 mL) were sequentially added through a septum sealing the top of the condenser. The reaction mixture was stirred at 65 °C for 5 h and then subjected to standard work-up. Chromatography of the crude product (hexanes:EtOAc 9:1 as eluent)

yielded 227 mg of **3.220** (72%) as clear oil, IR (film) (ν_{max} cm^{-1}) 2989, 2978, 1704, 1612, 1288, 1001; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, 1H, J = 7.6 and 2.0 Hz), 7.29-7.39 (m, 2H), 7.20 (dd, 1H, J = 8.0 and 0.8 Hz), 7.15 (s, 1H), 6.98 (s, 1H), 6.88 (s, 1H), 3.62 (q, 2H, J = 7.2 Hz), 3.45 (1, 2H, J = 7.2 Hz), 2.49 (s, 3H), 2.46 (s, 3H), 1.35 (t, 3H, J = 6.8 Hz), 1.24 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 153.8, 150.9, 148.0, 134.7, 130.3, 128.9, 127.7, 126.5, 125.7, 124.7, 124.3, 123.8, 108.7, 103.7, 42.1, 41.8, 21.8, 18.5, 14.3, 13.4; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 337 (16), 322 (26), 308 (64), 265 (34), 237 (55), 191 (36), 100 (100), 72 (82); HRMS calcd for $C_{21}H_{23}NO_3$ 337.1678, found 337.1673.

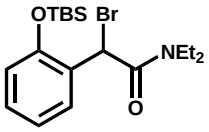
2-(2-(Tert-butyldimethylsilyloxy)phenyl)-*N*,*N*-diethylacetamide (3.244)



A solution of LDA was prepared by treating a stirred solution of DIPA (7.14 mL, 51 mmol) in THF (35 mL) at 0 °C with a solution of ^{n}BuLi (18.1 mL, 42.5 mmol, 2.35 M in hexanes). After stirring for 10 min at 0 °C, the LDA solution was cooled to –78 °C and a solution of TBSCl (3.5 g, 23.2 mmoL) in THF (53 mL) and neat **3.243** (4 g, 19.3 mmol) were sequentially added. The reaction mixture was stirred for 1 h at –78 °C, allowed to warm to 0 °C over 2 h and then stirred for an additional hour. Standard work-up and chromatography (hexanes/EtOAc 8.5/1.5 as eluent) yielded 5.21 g of **3.244** (84%) as a clear oil, IR (neat) ν_{max} 2958, 2930, 2854, 1645, 1600, 1582, 1495, 1258 cm^{1}; ^{1}NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, 1H, J = 7.4 and 1.5 Hz), 7.10 (dt, 1H, J = 7.5 and 1.8 Hz), 6.90 (dt, 1H, J = 7.5 and 1.8 Hz), 6.80 (dd, 1H, J = 7.4 and 1.5 Hz), 3.65 (s, 2H), 3.38 (q, 2H, J = 7.2 Hz), 3.22 (q, 2H, J = 7.2 Hz), 1.11 (t, 3H, J = 7.2 Hz), 1.03 (t, 3H, J = 7.2 Hz), 1.00 (s, 9H), 0.22 (s, 6H); ^{13}C

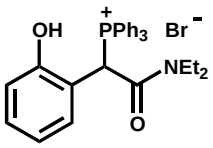
NMR (75 MHz, $CDCl_3$) δ 170.3, 152.6, 129.2, 127.4, 126.0, 121.1, 118.0, 41.9, 39.7, 34.8, 25.6, 17.8, 13.8, 12.5, -4.6; LRMS (EI, 70 eV) *m/z* (rel.intensity %) 322 (49), 321 (27), 306 (24), 264 (42), 165 (31), 100 (21), 72 (100); HRMS calcd for $C_{18}H_{32}NO_2Si$, 322.2202, found 322.2203.

2-Bromo-2-(2-(tert-butyldimethylsilyloxy)phenyl)-*N*,*N*-diethylacetamide (3.246)



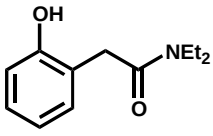
To a stirred solution of **3.244** (2.0 g, 6.20 mmol) in THF (25 mL) –78 °C, was added dropwise a solution of LDA (10.7 mL, 7.44 mmol, 0.7 M inTHF). After stirring for 30 min at this temperature, $BrCF_2CF_2Br$ (1.0 mL, 7.44 mL) was added dropwise and the mixture was stirred for 30 min at –78 °C. The reaction mixture was then allowed to warm to 0 °C and then quenched with a saturated aqueous NH_4Cl solution. Standard work-up and chromatography yielded 2.15 g of **3.246** (87%) as clear oil, IR (film) ν_{max} cm^{-1} 2972, 2967, 2838, 1654, 1585, 1579, 1495, 1273; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, 1H, *J* = 7.6 and 1.6 Hz), 7.19 (dt, 1H, *J* = 7.6 and 1.6 Hz), 6.96 (t, 1H, *J* = 8.0 Hz), 6.81 (d, 1H, *J* = 8.0 Hz), 6.25 (s, 1H), 3.48 (q, 1H, *J* = 6.8 Hz), 3.30-3.40 (m, 2H), 3.18 (q, 2H, *J* = 6.8 Hz), 1.11 (t, 3H, *J* = 6.8 Hz), 1.06 (s, 9H), 1.04 (t, 3H, *J* = 6.8 Hz), 0.33 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.4, 155.0, 133.3, 133.0, 130.8, 125.0, 121.3, 45.1, 44.3, 28.8, 21.3, 17.2, 16.0, -0.9, -1.2; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 401 (1), 399 (1), 386 (6), 384 (5), 344 (98), 342 (100), 283 (21), 285 (20), 269 (69), 267 (68); HRMS calcd for $C_{18}H_{30}BrNO_2Si$, 399.1229, found 399.1234.

***N*,*N*-Diethyl-2'-hydroxybenzylcarboxamide-triphenylphosphonium bromide (3.247)**



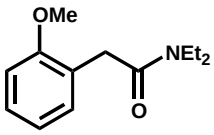
A 50 mL flask was charged with **3.246** (1.2 g, 3.01 mmol) and PPh_3 (1.18 g, 4.51 mmol) and their stirred solution in toluene (20 mL) was refluxed for 24 h. The solvent was removed *in vacuo* and the product was recrystallized (hexanes/EtOAc) to give 0.87 g of **3.247** (53%) as colourless crystals, mp 179-182 °C (toluene); IR (film) ν_{max} cm^{-1} 3448, 2870, 1632, 1438; ^1H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.6-7.82 (m, 15H), 7.18 (t, 1H, J = 6.5 Hz), 6.66-6.75 (m, 2H) 6.57 (t, 1H, J = 7.5 Hz), 5.30 (s, 1H), 3.43-3.53 (m, 1H), 3.33-3.43 (m, 2H), 3.02-3.11 (m, 1H), 0.92-1.10 (m, 3H), 0.76-0.87 (m, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.3, 154.8 (d, J = 6.2 Hz), 134.6 (d, J = 2.9 Hz), 134.3 (d, J = 9.4 Hz), 131.5, 129.8 (d, J = 12.5 Hz), 129.5 (d, J = 5 Hz), 119.5 (d, J = 25 Hz), 118.6 (d, J = 25 Hz), 112.5 (d, J = 5.6 Hz), LRMS (EI, 70 eV) *m/z* (rel. intensity %) 468 (100), 263 (10); HRMS calcd for $C_{30}H_{31}NO_2P$, 468.2092, found 468.2105.

***N*,*N*-Diethyl-2-(2-hydroxyphenyl)acetamide (3.248)**



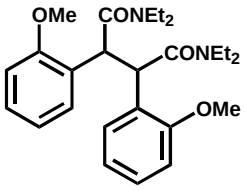
To a stirred solution of **3.244** (2.83 g, 8.80 mmol) in THF (40 mL) at −10 °C, was added TBAF (2.64 mL, 2.64 mmol, 1M in THF). After stirring at −10 °C for 15 min, the reaction mixture was quenched with a saturated aqueous Na_2CO_3 solution, subjected to standard work-up and chromatography (hexanes:EtOAc 8:2 as eluent) to yield 1.75 g of **3.248** (96%) as colourless solid whose ^1H and ^{13}C spectral data was found to be consistent with those reported for the authentic material.[110]

***N*,*N*-Diethyl-2-(2-methoxyphenyl)acetamide (3.249)**



To a stirred suspension of NaH (0.71 g, 17.7 mmol, 60% dispersion in mineral oil) in anhydrous THF (30 mL) cooled with an ice bath, was added dropwise a solution of **3.248** (3.5 g, 16.9 mmol) in THF (20 mL) while allowing the escape of H_2 through a vent. The reaction mixture was stirred and allowed to warm to rt over ~ 2 h (or until the evolution of H_2 completely ceased). MeI (1.16 mL, 18.6 mmol) was then added and, after stirring for 2 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. Standard work-up and chromatography yielded 3.54 g of **3.249** (95%) as clear oil, IR (film) ν_{max} cm^{-1} 2984, 2943, 2832, 1642, 1498, 1455, 1428, 1311, 1231, 1112; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17-7.23 (m, 2H), 6.90 (t, 1H, J = 7.5 Hz), 6.84 (d, 1H, J = 8.0 Hz), 3.79 (s, 3H), 3.65 (s, 2H), 3.38 (q, 2H, J = 7.0 Hz), 3.30 (1, 2H, J = 7.0 Hz), 1.12 (t, 3H, J = 7.0 Hz), 1.09 (t, 3H, J = 7.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.3, 156.5, 129.7, 127.6, 124.1, 120.3, 110.0, 55.0, 42.0, 39.8, 34.2, 13.9, 12.7; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 221 (67), 190 (8), 121 (20), 100 (100), 91 (42), 72 (72); HRMS calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1417.

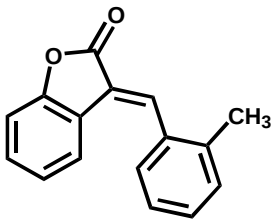
***N*^{1},*N*^{1},*N*^{4},*N*^{4}-Tetraethyl-2,3-bis(2-methoxyphenyl)succinamide (3.250)**



To a stirred solution of **3.249** (0.10 g, 0.45 mmol) in anhydrous THF (3 mL) at −78 °C, was added a solution of LDA (0.71 mL, 0.50 mmol, 0.7 M in THF). The reaction mixture was stirred for 30 min at this temperature and $BrCF_2CF_2Br$ (1.0 mL, 7.44 mL) was added dropwise. The reaction mixture was stirred for an additional 30 min at −78 °C, allowed to warm to 0 °C

and was then quenched with a saturated aqueous NH_4Cl solution. Standard work-up and chromatography (hexanes:EtOAc 7:3 as eluent) yielded 0.084 g of **3.250** (85%) as a colourless solid, mp 164-165 °C; IR (film) ν_{max} cm^{-1}2977, 2935, 2836, 1641, 1491, 1464, 1430, 1248, 1138, 1098, 1028, 764; ^1H NMR (400 MHz, $CDCl_3$) δ7.46 (dd, 1H, J = 7.6 and 2.0 Hz), 6.99 (dt, 1H, J = 7.6 and 1.6 Hz), 6.80 (dt, 1H, J =7.6 and 1.2 Hz), 6.42 (dd, 1H, J = 7.6 and 1.2 Hz), 5.10 (s, 1H), 3.48 (sex, 1H, J = 6.8 Hz), 3.23-3.32 (m, 4H), 3.09-3.18 (m, 2H), 1.04 (t, 3H, J = 7.2 Hz), 1.02 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ173.0, 156.7, 130.0, 127.8, 126.5, 120.2, 109.9, 55.4, 44.4, 41.9, 40.6, 14.2, 13.1; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 440 (M^+, 13), 368 (72), 340 (32), 192 (100), 100 (95), 72 (56); HRMS calcd for $C_{26}H_{36}N_2O_4$ 440.2675, found 440.2669.

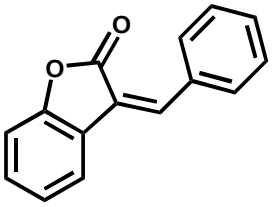
(*E*)-3-(2-Methyl-benzylidene)-3H-benzofuran-2-one (*E*-3.253)



A 100 mL flask was charged with **3.252** (3.5 g, 26 mmol), 2-methylbenzaldehyde (3.02 mL, 26 mmol), PTSA·H_2O (0.643 g, 3.38 mmol) and anhydrous toluene (40 mL). After stirring at reflux for 12 h, the reaction mixture was washed with a saturated aqueous Na_2CO_3 solution, brine, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography of the crude material (hexanes:EtOAc 9:1) gave 5.1 g of **3.253** (83%, brown oil) as an inseparable 3:1 *E*/*Z* mixture (^1H NMR analysis). Distillation of this mixture under reduced pressure (Kugelrohr, 135 °C/0.1 mmHg) yielded a fraction (2.1 g) enriched in the *E* stereoisomer of **3.253** (*E*/*Z* 20:1, ^1H NMR analysis) which, over long storage at rt (1 year) became stereoisomerically pure and solid, IR (film) ν_{max} cm^{-1} 2358, 1786, 1634, 1611, 1459, 1147, 1133, 1079; ^1H NMR (400 MHz, $CDCl_3$) δ7.96 (s, 1H),

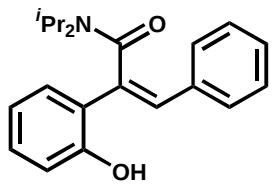
7.63 (d, 1H, J = 7.2 Hz), 7.41 (d, 1H, J = 8.0 Hz), 7.37 (d, 1H, J = 6.8 Hz), 7.26-7.35 (m, 3H), 7.12 (d, 1H, J = 8.4 Hz), 6.97 (dt, 1H, J = 8.0 and 0.8 Hz), 2.38 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.7, 154.4, 140.0, 137.8, 133.2, 130.9, 130.8, 130.4, 128.2, 125.9, 123.7, 123.0, 122.9, 122.0, 111.1, 19.9; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 236 (100), 235 (36), 221 (20), 219 (30), 207 (91), 178 (45); HRMS calcd for $C_{16}H_{12}O_2$, 236.0837, found 236.0847.

(*Z*)-3-Benzylidene-3H-benzofuran-2-one (*Z*-3.255)

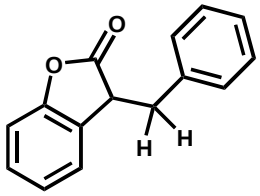


This compound was prepared according to a literature procedure and its ^{1}H spectral data were found to be consistent with the partial data reported,[88e] mp 104-105 (hexanes); IR (film) ν_{max} cm^{-1} 1769, 1624, 1463, 1383, 1231, 1113, 1042, 745; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.24 (m, 2H), 7.66 (s, 1H), 7.58 (d, 1H, J = 7.5 Hz), 7.47-5.74 (m, 3H), 7.36 (dt, 1H, J = 8.0 and 1.0 Hz), 7.21 (dt, 1H, J = 15 and 1.0 Hz), 7.14 (d, 1H, J = 8.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.8, 153.0, 140.3, 133.1, 132.0, 131.3, 129.9, 128.6, 125.4, 123.7, 120.8, 119.4, 110.8; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 222 (100), 221 (35), 194 (54), 165 (92); HRMS calcd for $C_{15}H_{10}O_2$, 222.0681, found 222.0684.

(*Z*)-2-(2-Hydroxyphenyl)-*N*,*N*-diisopropyl-3-phenylacrylamide (*Z*-3.256) and 3-Benzylbenzofuran-2(3H)-one (3.257)



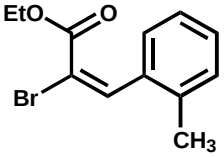
***Z*-3.256**



3.257

To a stirred solution (−78 °C) of **3.255** (100 mg, 0.45 mmol) in anhydrous THF (5 mL) at −78 °C was added a solution of LDA (0.70 mL, 0.5 mmol, 0.7M in THF). After stirring for 30 min at −78 °C, the reaction mixture was allowed to warm to −10 °C and quenched with a saturated aqueous NH_4Cl solution. Standard work-up and chromatography (hexanes/EtOAc 9.75/0.25 as eluent) yielded 70 mg of ***Z*-3.256** (48%), mp 214-215 °C (hexanes/EtOAc, lit[91] mp 215-217 °C) and 47 mg of **3.257** (47%), mp 55-57 (hexanes, lit[111] mp 57 °C). The analytical data obtained for these compounds was found consistent with that of the known materials.

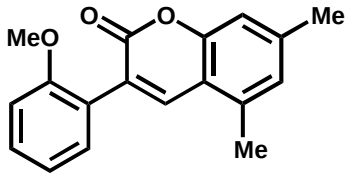
(*E*)-Ethyl 2-bromo-3-o-tolylacrylate (*E*-3.260)



A solution of *o*-tolylzinc chloride (**3.259**) was prepared by a literature procedure.[112] Thus, a stirred solution of 2-bromotoluene (1.56 mL, 13.02 mmol**)** in THF (20 mL) at −78 °C was treated with a solution of ^{t}BuLi (16.6 mL, 27.3 mmol, 1.65M in pentane). After stirring for 20 min at this temperature, a solution of $ZnCl_2$ (15.6 mL, 15.6 mmol, 1M in anhydrous THF) was added and the reaction mixture was allowed to warm to rt. After stirring for 20 min, the solution was added dropwise to a mixture of **3.258** (1.30 mL, 9.30 mmol) and $Pd(PPh_3)_4$ (0.54 g, 0.46 mmol) in THF (10 mL) at rt and the resulting solution was stirred for 4 h. Standard work-up and chromatography yielded 0.575 g of ***E*-3.260** (23%) as a clear oil,

IR (KBr) (ν_{max} cm^{-1}) 2981, 1726, 1613, 1482, 1367, 1258, 1218, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.65 (d, 1H J = 7.2 Hz), 7.20-7.31 (m, 3H), 4.35 (q, 2H, J = 7.2 Hz), 2.31 (s, 3H), 1.39 (t, 3H, J = 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.1, 140.7, 137.0, 133.7, 130.2, 129.9, 129.4, 128.7, 128.6, 128.0, 125.6, 115.7, 62.8, 19.9, 14.2; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 270 (14), 268 (14), 225 (38), 223 (35), 189 (62), 161 (91), 144 (40), 116 (57), 115 (100); HRMS calcd for $C_{12}H_{13}BrO_2$, 268.0099, found 268.0103.

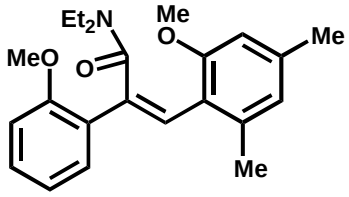
3-(2-Methoxyphenyl)-5,7-dimethyl-2H-chromen-2-one (3.270)



A flame-dried 250 mL flask was charged with 2'-methoxy-phenylacetic acid (5.0 g, 30.1 mmol) and thionyl chloride (11 mL, 150.4 mol) and the resulting solution was stirred at rt for 4 hours. Upon removal of the volatile components *in vacuo*, the crude acyl chloride **3.269** was dissolved in acetone (150 mL) and to this stirred solution were sequentially added **3.268**[113] (2.05 g, 13.7 mmol) and K_2CO_3 (41.46 g, 0.3 mol). The mixture was refluxed for 14 h and subjected to filtration through a sintered funnel. The K_2CO_3 cake was washed with acetone (300 mL) and the combined organic layers were concentrated *in vacuo* to give a residue which, upon recrystallization from MeOH, gave 3.76 g of **3.270** (98%) as a colourless solid, mp 129-133 °C (MeOH); IR (film) ν_{max} 1732, 2835, 2946 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.36-7.6 (m, 2H), 6.98-7.07 (m, 3H), 6.94 (s, 1H), 3.84 (s, 3H), 2.49 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 157.3, 151.4. 142.1, 138.8, 135.6, 130.9, 130.1, 126.9, 124.8, 124.7, 120.7, 115.9, 114.7, 111.4, 55.8, 21.7, 18.3; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 281 (M+H

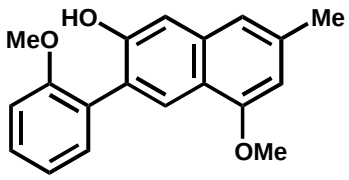
16), 280 (M^+, 71), 263 (32), 209 (48), 194 (36), 178 (47), 166 (50), 165 (100), 152 (34), 139 (31), 115 (59), 91 (44); HRMS calcd for $C_{18}H_{16}O_3$ 280.1099, found 280.1111.

(*Z*)-*N*,*N*-Diethyl-3-(2-methoxy-4,6-dimethylphenyl)-2-(2-methoxyphenyl)acrylamide (*Z*-3.271)



To a stirred solution of **3.270** (2.0 g, 7.13 mmol) in anhydrous THF (40 mL) at 0 °C, was added a solution of $LiNEt_2$ (27.5 mL, 9.27 mmol, 0.33 M in THF). The reaction mixture was stirred for 2 h at 0 °C and then for an additional 2 h at rt. After cooling the mixture to 0 °, MeI (4.4 mL, 71.3 mmol) and NaH (0.57 g, 14.26 mmol, 60% dispersion in mineral oil) were sequentially added and the mixture was allowed to warm to rt. After stirring for 12 hour, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and the crude mixture was subjected to standard work-up and chromatography (hexanes/EtOAc 3:1 as eluent) to yield 2.12 g of ***Z*-3.271** (81%) as a colourless solid, mp 145-147 °C (hexanes/EtOAc); IR (film) ν_{max} 1626, 2871, 2934, 2966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 1H, J = 7.2 Hz), 7.28 (t, 1H, J = 8.0 Hz), 6.98 (t, 1H, J = 8.0 Hz), 6.88 (d, 1H, J = 8.4 Hz), 6.77 (s, 1H), 6.62 (s, 1H), 6.51 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.59 (q, 2H, J = 7.2 Hz), 3.21 (q, 2H, J = 6.8 Hz), 2.64 (s, 3H), 2.24 (s, 3H), 0.93 (t, 3H, J = 7.2 Hz), 0.56 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 157.2, 156.0, 138.1, 137.2, 130.6, 129.7, 128.9, 127.7, 123.1, 122.2, 120.9, 111.0, 108.5, 55.4, 55.1, 42.1, 37.7, 21.6, 20.3, 12.7, 12.1; LRMS (EI, 70 eV) *m/z* (rel. intensity %) 367 (10), 352 (8), 336 (96), 295 (100), 267 (14), 159 (28); HRMS calcd for $C_{23}H_{29}NO_3$, 367.2147, found 367.2151.

5-Methoxy-3-(2-methoxyphenyl)-7-methylnaphthalen-2-ol (3.272)



To a stirred solution of ***Z*-3.271** (2.12 g, 5.76 mmol) in anhydrous THF (60 mL) at −78 °C was added a solution of LiTMP (11.11 mL, 7.78 mmol, 0.7 M in THF). The purple solution that instantaneously resulted was stirred at this temperature for 30 min and was allowed to warm to rt. After stirring for an additional 20 min at rt, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and was subjected to standard work-up. Chromatography of the crude material (hexanes : EtOAc 4:1 as eluent) yielded 1.64 g of **3.272** (95%) as a light brown solid, mp 111-114 °C (hexanes/EtOAc); IR (film) ν_{max} 1638, 2835, 2937, 3403 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.48 (dd, 1H, J = 7.6 and 1.6 Hz), 7.43 (dt, 1H, J = 7.6 and 1.6 Hz), 7.29 (s, 1H), 7.17 (dt, 1H, J = 8.0 and 0.4 Hz), 7.15 (s, 1H), 7.07 (d, 1H, J = 8.0 Hz), 6.54 (s, 1H), 6.17-6.42 (bs, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.6, 152.6, 136.6, 136.0, 133.1, 129.5, 127.5, 126.9, 125.0, 122.3, 119.5, 117.9, 111.6, 111.2, 104.3, 56.3, 55.4, 31.6, 22.4; (EI, 70 eV) *m/z* (rel. intensity %) 294 (100), 251 (10), 207 (11), 165 (9); HRMS calcd for $C_{19}H_{18}O_3$, 294.1256, found 294.1268.

3.7. References

[1] Gould, S.J. *Chem. Rev.* **1997**, *97*, 2499-2509.

[2] Hasinoff, B.B.; Wu, X.; Yalowich, J.C.; Goodfellow, V.; Laufer, R.S.; Adedayo, O.; Dmitrienko, G.I. *Anti-Cancer Drugs* **2006**, *17*, 825-837.

[3] a) Ito, S.; Matsuya, T.; Omura, S.; Otani, M.; Nakagawa, A.; Takeshima, H.; Iwai, Y.; Ohtani, M.; Hata, T. *J. Antibiot.* **1970**, *23*, 315-317. b) Hata, T.; Omura, S.; Iwai, Y.; Nakagawa, A.; Otani, M. *J. Antibiot.* **1971**, *24*, 353-359. c) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1971**, *19*, 2428-2430. d) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm Bull.* **1973**, *21*, 931-940. e) Furusaki, A.; Matsui, M. Watanabe, T.; Omura, S.; Nakagawa, A.; Hata, T. *Isr. J. Chem.* **1972**, *10*, 173-.

[4] Young, J.-J.; Ho, S.-N.; Ju, W.-M.; Chang, L.-R. *J. Antibiot.* **1994**, *47*, 681-687.

[5] Seaton, P.J.; Gould, S.J. *J. Am. Chem. Soc.* **1988**, *110*, 5912-5914.

[6] Dmitrienko, G.I.; Nielsen, K.E.; Steingart, C.; Ming, N.S.; Willson, J.M.; Weeratunga, G. *Tetrahedron Lett.* **1990**, *31*, 3681-3684.

[7] Echavarren, A.M.; Tamayo, N.; Parades, M.C. *Tetrahedron Lett.* **1993**, *34*, 4713-4716.

[8] a)Gould, S.J.; Tamayo, N.; Melville, C.R.; Cone, M.C. *J. Am. Chem. Soc.* **1994**, *116*, 2207-2208. b) Mithani, S.; Weeratunga, G.; Taylor, N.J.; Dmitrienko, G.I. *J. Am. Chem. Soc.* **1994**, *116*, 2209-2210.

[9] Hauser, F.; Zhou, M.J. *J. Org. Chem.* **1996**, *61*, 5722-5723.

[10] Gould, S.J.; Chen, J.; Cone, M.C.; Gore, M.P.; Melville, C.R.; Tamayo, N. *J. Org. Chem.* **1996**, *61*, 5720-5721.

[11] Proteau, P.J.; Yonfu, Li; Chen, J.; Williamson, R.Y.; Gould, S.J.; Laufer, R.; Dmitrienko, G.I. *J. Am. Chem. Soc.* **2000**, *122*, 8325-8326.

[12] He, H.; Ding, D.W.; Bernan, V.S.; Richardson, A.D.; Ireland, C.M.; Greenstein, M.; Ellestad, G.A.; Carter, G.T. *J. Am. Chem. Soc.* **2001**, *123*, 5362-5363.

[13] Krygowski, E.S.; Murphy-Benenato, K.; Shair, M.D. *Angew. Chem. Int. Ed.* **2008**, *47*, 1680-1684.

[14] Sato, Y.; Gould, S.J. *Tetrahedron Lett.* **1985**, *26*, 4023-4026.

[15] Seaton, P.J.; Gould, S.J. *J. Am. Chem. Soc.* **1987**, *109*, 5282-5284.

[16] Gould, S.J.; Shen, B.; Whittle, Y.G.; *J. Am. Chem. Soc.* **1989**, *111*, 7932-7938. Gould, S.J.; Kirchmeier, M.J.; LaFever, R.E. *J. Am. Chem. Soc.* **1996**, *118*, 7663-7666.

[17] Moore, H.W. *Science* **1977**, *197*, 527-532.

[18] Imae, K.; Nihei, Y.; Oka, M.; Yamasaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1993**, *46*, 1031-1033. Fusari, S.; Haskell, T.H.; Frohardt, R.P.; Bartz, Q.R. *J. Am. Chem. Soc.* **1954**, *76*, 2881-2883. Dion, H.W.; Fusari, S.; Jakubowski, Z.L.; Zora, J.G.; Bartz, Q.R. *J. Am. Chem. Soc.* **1976**, *78*, 3075-3077. Fukuda, D.S.; Mynderse, J.S.; Baker, P.J.; Berry, D.M.; Boeck, L.D.; Yao, R.C.; Mertz, F.P.; Nakatzukasa, W.M.; Mabe, J.; Ott,

J.; Counter, F.T.; Ensminger, P.W.; Allen N.E.; Alborn W.E.; Hobbs, J.N. *J. Antibiot.* **1990**, *43*, 623-633.

[19] Arya, D.P.; Jebaratnam, D.J. *J. Org. Chem.* **1995**, *60*, 3268-3269.

[20] Zeng, W.; Ballard, E.T.; Tkachenko, A.G.; Burns, V.A.; Feldheim, D.L.; Melander, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5148-5151.

[21] Laufer, R.S.; Dmitrienko, G.I. *J. Am. Chem. Soc.* **2002**, *124*, 1854-1855.

[22] Feldman, K.S.; Eastman, K.J. *J. Am.Chem. Soc.* **2006**, *128*, 12562-12573.

[23] O'Hara, K.A.; Wu, X.; Patel, D.; Liang, H.; Yalowich, J.C.; Chen, N.; Goodfellow, V.; Adedayo, O.; Dmitrienko, G.I.; Hasinoff, B.B. *Free Rad. Biol. Med.* **2007**, *43*, 1132-1144.

[24] Chen, N.; Carrière, M.B.; Laufer, R.S.; Taylor, N.J.; Dmitrienko, G.I. *Org. Lett.* **2008**, *10*, 381-384.

[25] Lei, X.; Porco, J.A.Jr. *J. Am. Chem. Soc.* **2006**, *128*, 14790-14791.

[26] Nicolaou, K.C.; Li, H.; Nold, A.L.; Pappo, D.; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356-10357.

[27] Kumamoto, T.; Kitani, Y.; Tsuchiya, H.; Yamaguchi, K.; Seki, H.; Ishikawa, T. *Tetrahedron* **2007**, *63*, 5189-5199.

[28] Gould, S.J.; Melville, C.R.; Cone, M.C.; Chen, J.; Carney, J.R. *J. Org. Chem.* **1997**, *62*, 320-324.

[29] Gould, S.J.; Melville, C.R. *Bioorg. Med. Chem. Lett.*. **1995**, *5*, 51-54.

[30] Birman, V.B.; Zhao, Z.; Guo, L. *Org. Lett.* **2007**, *9*, 1223-1225.

[31] Mohri, S.-i.; Stefinovich, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072-7073.

[32] Qabaja, G.; Jones, G. *Tetrahedron Lett.* **2000**, *41*, 5317-5320.

[33] Wang, J.-X.; McCubbin, J.A.; Jin, M.; Laufer, R.S.; Mao, Y.; Crew, A.P.; Mulvihill, M.J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923-2926 and references therein.

[34] González-Cantalapietra, E.; de Frutos, Ó.; Atienza, C.; Mateo, C.; Echavarren, A.M. *Eur. J. Org. Chem.* **2006**, 1430-1443.

[35]Schneider, K.; Nicholson, G.; Ströbele, M.; Baur, S.; Niehaus, S.; Fiedler, H.P.; Süssmuth, R.D. *J. Antibiot.* **2006**, *59*, 105-109. Akiyama, T.; Nakamura, K.T.; Takahashi, Y.; Naganawa, H.; Muraoka, Y.; Aoyagi, T.; Takeuchim T. *J. Antibiot.* **1998**, *51*, 586-588.

[36] Seaton, P.J.; Gould, S.J. *J. Antibiot.* **1989**, *42*, 189-197.

[37] Liu, W.; Buck, M.; Chen, N.; Shang, M.; Taylor, N.J.; Asoud, J.; Wu, X.; Hasinoff, B.B.; Dmitrienko, G.I. *Org. Lett.* **2007**, *9*, 2915-2918.

[38] For a comparison, Lomaiviticin A and B exhibit IC_{50} values ranging between 7 pM and 0.7 nM , while active kinamycins generally display submicromolar IC_{50} values.

[39] Reed, J.N.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 3795-3798.

[40] Khatib, S.; Bouzoubaa, M.; Coudert, G. *Tetrahedron Lett.* **1998**, *39*, 989-990.

[41] Reed, M.A.; Chang, M.T.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2297-2300.

[42] Reed, M.A. unpublished data.

[43] Negishi, E.-i.; King, A.O.; Klima, W.L. *J. Org. Chem.* **1980**, *2*, 193-196.

[44] Kalinin, A.V.; Scherer, S.; Snieckus, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 3399-3404.

[45] Bassindale, A.R.; Glynn, S.J.; Taylor, P.G. in: *The Chemistry of Organic Silicon Compounds*, Vol. 2 (Eds.: Patai, S.; Rappoport, Z. and Apeloig, Y.), John Wiley & Sons, New York, **1998**. Brinkman, E.A.; Berger, S.; Brauman, J.I. *J. Am. Chem. Soc.* **1994**, *116*, 8304-8310 and references therein.

[46] Gavin, J.P.; Waigh, R.D. *J. Chem. Soc., Perkin Trans. 1* **1990**, 503-508.

[47] Molander, G.A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286.

[48] Li, G. *J. Organometal. Chem.* **2002**, *653*, 63-68.

[49] James, A.C.; Snieckus, V. *Tetrahedron Lett.* **1997**, *38*, 8149-8152; James, A.C. Ph.D. Thesis, University of Waterloo, Canada, 1998.

[50] Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424-426.

[51] Unpublished results.

[52] Siegrist, A.E.; Liechti, P.; Meyer, H.R.; Weber, K. *Helv. Chim. Acta* **1969**, *52*, 2521-2554. Gassman, P.; Mass, S. *Helv. Chim. Acta* **1980**, *63*, 1311-1334. Skibniewski, A.; Bluet, G.; Druzé, N.; Riant, O. *Synthesis* **1999**, *3*, 459-462. Gégout, A.; Figueira-Duarte, T.M.; Nierengarten, J.-F.; Listorti, A.; Armaroli, N. **2006**, *18*, 3095-3099. Yu, R.; Yakimansky, A.; Voigt-Martin, I.G.; Fetten, M.; Schnorpfeil, C.; Schollmeyer, D.; Meier, H *J. Chem. Soc., Perkin Trans. 2* **1999**, 1881-1890.

[53] Kendall, C.N.O., M.Sc. Thesis, Queen's University, Kingston, Canada, 2000.

[54] Personal communication.

[55] Whisler, M.C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206-2225.

[56] Hogan, A.-M.L.; O'Shea, D.F. *J. Org. Chem.* **2007**, *72*, 9557-9571.

[57] Macklin, T.K. Ph.D. Thesis, Queen's University, Kingston, Canada, 2007.

[58] Katritzsky, A.R.; Fan, W.-Q.; Akutagawa, K. *Tetrahedron* **1986**, *42*, 4027-4034.

[59] Kessler, A.; Coleman, C.M.; Charoenying, P.; O'Shea, D.F. *J. Org. Chem.* **2004**, *69*, 7836-7846. Coleman, C.M.; O'Shea, D.F. *J. Am. Chem. Soc.* **2003**, *125*, 4054-4055.

[60] Hogan , A.-M.L.; O'Shea, D.F. *J. Am. Chem. Soc.* **2006**, *128*, 10360-10361.

[61] Mpango, G.B.; Mahalanabis, K.K.; Mahdavi-Damghani, Z.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4823-4826.

[62] Bermand, N.; Marek, I.; Normant, J.F. *Tetrahedorn Lett.* **1999**, *40*, 3379-3382.

[63] Basavaiah, D.; Venkateswara, R.K.; Jannapu, R.R. *Chem. Soc. Rev.* **2007**, *36*, 1581-1588.

[64] Hoffman, R.W.; Brönstrup, M.; Müller, M. *Org. Lett.* **2003**, *5*, 313-316.

[65] Rossi, R.; Carpita, A. *Tetrahedron Lett.* **1986**, *27*, 2529-2532.

[66] Xu, C.; Negishi, E.-i. *Tetrahedron Lett.* **1999**, *40*, 431-434.

[67] Minato, A.; Suzuki, K. Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257-1258.

[68] Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873-8879.

[69] Shen, W. *Synlett* **2000**, 737-739.

[70] Minato, A. *J. Org. Chem.* **1991**, *56*, 4052-4056.

[71] Winship, K.A. *Adverse Drug React Acute Poisoning Rev.* 1988, *7*, 19-38.

[72] Kraus, G.A.; Zhao, G. *J. Org. Chem.* **1996**, *61*, 2770-2773.

[73] Ramirez, F.; Desai, N.B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745-1747. Huh, D.H.; Jeong, J.S.; Lee, H.B.; Ryu, H.; Kim, Y.G. *Tetrahedron* **2002**, *58*, 9925-9932. For an improved procedure not using PPh_3 procedure see Fang, Y.-Q.; Lifchits, O.; Lautens, M. *Synlett* **2008**, 413-417.

[74] a) Roush, W.R.; Moriarty, K.J.; Brown, B.B. *Tetrahedron Lett.* **1990**, *31*, 6509-6512. b) Roush, W.R.; Reilly, M.L.; Kayama, K.; Brown, B.B. *J. Org. Chem.* **1997**, *62*, 8708 and references cited therein. c) Baldwin, J.E.; Chesworth, R. Paker, J.S.; Russel, A.T. *Tetrahedron Lett.* **1995**, *36*, 9551-9554.

[75] Galván-Arzate, S.; Santamaria, A. *Toxicol. Lett.* **1998**, *99*, 1-13.

[76] Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907-910.

[77] Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955-2958.

[78] Dieck, H.A.; Heck, F.R. *J. Organomet. Chem.* **1975**, *93*, 259-263.

[79] Rutherfor, J.L.; Rainka, M.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 15168-15169. Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764-765.

[80] Tao, W.; Silverberg, L.J.; Rheingold, A.L.; Heck, R.F. *Organometallics* **1989**, *8*, 2550-2559.

[81] Wang, L.; Shen, L. *Tetrahedron Lett.* **1998**, *39*, 7625-7628. For other examples of Pd(II)-catalyzed dealkylations see: Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2003**, *5*, 2441-2444; Ref. 76; Shen, W.; Thomas, S.A. *Org. Lett.* **2000**, *2*, 2857-2860.

[82] Kalinin, A.V.; Miah, M.A.J.; Chattopadhyay, S.; Tsukazaki, M.; Wicki, M.; Nguen, T.; Coelho, A.L.; Kerr, M.; Snieckus, V. *Synthesis* **1997**, 839-841.

[83] Kira, M.; Iwamoto, T. in *Chemistry of Organic Silicon Compounds*, *Vol. 3,* Wiley, New York, **2001**, p. 853-948.

[84] Habata, Y.; Akabori, S.; Sato, M. *Bull. Chem. Soc. Jpn* **1985**, *58*, 3540. Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 4879-4882.

[85] Csákÿ, A.G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313-320.

[86] Sharma, V.; Tepe, J.J. *Org. Lett.* **2005**, *7*, 5091-5094. Sweeney, J.B.; Tavassoli, A.; Carter, N.B.; Hayes, J.F. *Tetrahedron* **2002**, *58*, 10113-10126.

[87] Lardic, M.; Patry, C.; Duflos, M.; Guillon, J.; Massip, S.; Cruzalegui, F.; Edmonds, T.; Giraudet, S.; Marini, L.; Leonce, S. *J. Enz. Inhib. Med. Chem.* **2006**, *21*, 313-325.

[88] a) Rizzi, E.; Dallavalle, S.; Merlini, L.; Beretta, G.L.; Pratesi, G.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4313-4316. b) Venkateswarlu, S.; Panchagnula, G.K.; Guraiah, M.B.; Subbaraju, G.V. *Tetrahedron* **2006**, *62*, 9855-9860 and c) **2005**, *61*, 3013-3017. d) Gadre, S.Y., Marathe, K.G. *Synth. Commun.* **1988**, *18*, 1015-1027. e) Msaddek, M.; Rammah, M.; Ciamala, K.; Vebrel, J.; Laude, B. *Synthesis* **1997**, 14951498.

[89] Dätwyler, P.; Bosshardt, H.; Bernhard, H.O.; Hesse, M.; Jonhe, S. *Helv. Chim. Acta* **1978**, *61*, 2646-2671.

[90] Rossi, R.; Bellina, F.; Carpita, A.; Gori. R. *Gazz. Chim. Ital.* **1995**, *125*, 381-392.

[91] I am deeply indebted to Dr. Patel for the new momentum he has given to this project and the work he has independently carried out during the preparation of this thesis.

[92] Costa, A.M.B.S.R.C.S.; Dean, F.M.; Jones, M.A.; Varma, R. *J. Chem. Soc. Perkin Trans. 1* **1985**, 799-808.

[93] Pulla Rao, P.; Srimannarayana, G. *Synthesis* **1981**, 887-888.

[94] See Section 1.1.6 and references therein.

[95] Patel, J.; Snieckus, V. work in progress, 2008.

[96] Wolfe, J.P.; Ahman, J.; Sadighi, J.P.; Singer, R.A.; Buchwald, S.L. *Tetrahedron Lett.* **1997**, *38*, 6367-6370.

[97] Sammes, P.G.; Dodsworth, D.J. *Chem. Commun.* **1979**, *1*, 33-34.

[98] The phenoxide-directed *ortho*-lithiation followed by electrophilic quench with MeI, CO_2, $(PhCO)_2O$ and CBr_4 has been demonstrated to occur in 42-48 yield%, Posner, G.H.; Canella, K.A. *J. Am. Chem. Soc.* **1985**, *107*, 2571-2573.

[99] Mills, R.J.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1565-1568. Mills, R.J.; Taylor, N.J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372-4385.

[100] Zhao, Z.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2523-2526 and **2006**, *8*, 4173-4173.

[101] We thank Dr. Nicholas Mosey for his prompt collaboration on this topic.

[102] Reed, J.N.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 3795-3798.

[103] a) For "stabase" see: Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787-1790. b) For "benzostabase" see: Bonar-Law, R.P.; Davis, A.P.; Dorgan, B.J. *Tetrahedron Lett.* **1990**, *31*, 6721-6724 and 6725-6728. c) For TEDI derivatives see: Davis, A.P.; Gallagher, P.J. *Tetrahedron Lett.* **1995**, *36*, 3269-3272.

[104] Kalinin, A.V.; Reed, M.A.; Norman, B.H.; Snieckus, V. *J. Org. Chem.* **2003**, *68*, 5992-5999.

[105] **3.125** was prepared according to a literature procedure: Weeratunga, G.; Jaworska-Sobiesiak, A.; Horne, S.; Rodrigo, R. *Can J. Chem.* **1987**, *65*, 2019-2023.

[106] **3.145** was purchased from Acros Organics.

[107] Harder, S.; Boersma, J.; Brandsma, L. *Organomet.*, **1990**, *9*, 511-516.

[108] Truce, W.E; Lin, C.-I. N. *J. Am. Chem. Soc.* **1973**, *95*, 4426-4428.

[109] Verkerk, U.; Fujita, M.; Dzwiniel, T.L.; McDonald, R.; Stryker, J.M. *J. Am. Chem. Soc.* **2002**, *124*, 9988-9989.

[110] Miah, M.A.J., PhD. Thesis, University of Waterloo, Waterloo, Canada, 1985.

[111] Yoneda, E.; Sugioka, T.; Hirao, K.; Zhang, S.-W.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 477-484.

[112] Negishi, E.; Takahashi, T.; King, A.O. *Org. Synth.* **1988**, *66*, 67-74.

[113] **3.268** was prepared according to a literature procedure: Knight, P.D.; Klarkson, G.; Hammond, M.L.; Kimberley, B.S.; Scott, P. *J. Organomet. Chem.* **2005**, *690*, 5125-5144.

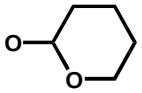
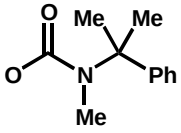
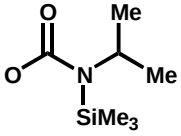
CHAPTER 4

Studies Concerning the Tetraethylphosphorodiamidate Directed Metalation Group

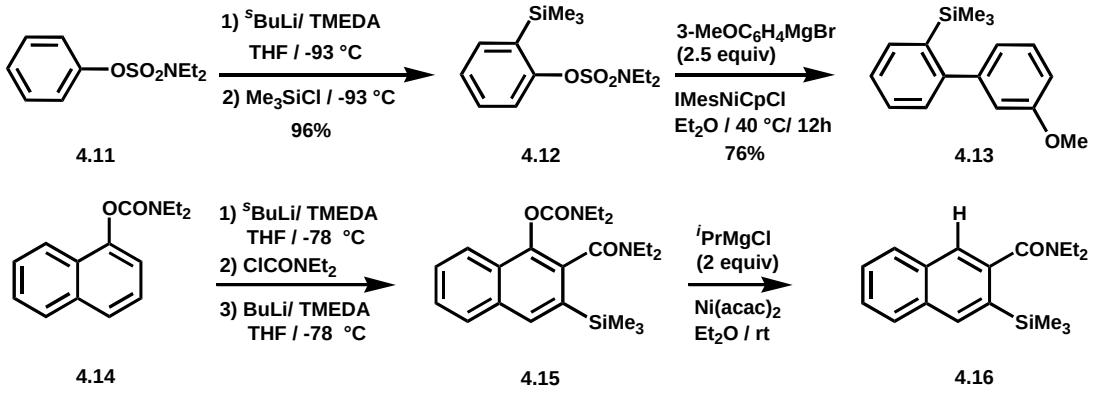
4.1 *O*-Based Directed Metalation Groups

Within the class of *O*-based DMGs for the D*o*M reaction, the OMOM,[1] OTHP[2] and the OSEM[3] groups (**4.2**, **4.3** and **4.4**, respectively), borrowed from the realm of known phenol protecting groups, are established DMGs (Table 4.1). Due to their acetal nature, they do not suffer the chemical attack of strong bases even at relatively high temperatures (0 °C - rt); in contrast, their sensitivity to mild acidic conditions allows their selective removal, a possibility that greatly widens their synthetic applicability. Thus, while taking on an active role as DMGs, they maintain their vocation of temporary masking groups, functional only to the synthesis of *o*-substituted phenols. In particular, the use of the moderately strong OMOM group in D*o*M has become a routine practice in synthetic organic chemistry.[4]

Table 4.1. Common *O*-Based Directed Metalation Group

OCH_3	4.1 (Gilman-Wittig, 1938)[5]	OSO_2NEt_2	4.7 (Snieckus, 2005)[7]
OCH_2OCH_3	4.2 (Christensen, 1975)[1]	$OCONEt_2$	4.8 (Snieckus, 1983)[6]
	4.3 (Cassidy, 1957)[2]		4.9 (Snieckus, 1999)[8]
$OCH_2OCH_2SiMe_3$	4.4 (Snieckus, 1990)[3]		
$OPO(OEt)_2$	4.5 (Melvin, 1981)[12a]		4.10 (Hoppe, 2001)[9]
$OPO(NMe_2)_2$	4.6 (Näsman, 1986)[17]		

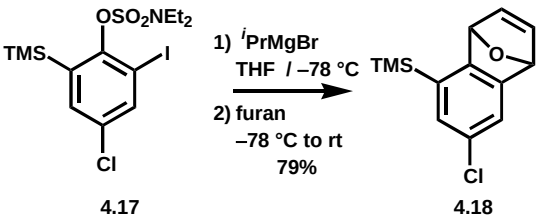
On the contrary, other groups resisting hydrolytic cleavage have naturally developed in other directions and beyond the DMG role. Thus, by acting as leaving groups in the Kumada-Corriu cross coupling reaction, the diethyl *O*-carbamate (**4.8**)[6] and diethyl *O*-sulfamate (**4.7**)[7] groups have consolidated the proactive nexus between the D*o*M reaction and the transition metal-catalyzed coupling chemistry while, at the same time, earning the exclusive title of latent DMGs (Scheme 4.1).



Scheme 4.1

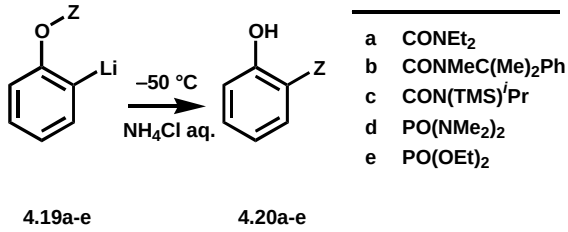
Suitably located between these two sets of DMGs are the *N*-cumyl and the *N*-TMS *O*-carbamate groups (**4.9**[8] and **4.10**[9], Table 4.1) which were designed with the aim of combining the strong directing power distinctive of the carbamate group and the potential of mild deprotection offered by their ready cleavage to secondary *O*-carbamates. The cleavage of the latter to phenols and isocyanates is also a well known and facile process. All *O*-based DMGs containing a polarized π-system require carefully controlled conditions to avoid undesired reactions leading to the modification of the directing group. To illustrate, unless the metalation of an aryl *O*-sulfamate is carried out at –93 °C, the DMG is ejected with formation of a benzyne as evidenced by a furan trapping experiment (**4.17**→**4.18**, Scheme 4.2).[10] For the other groups, D*o*M results in a 1,3 *O*→*C* migration

of the electrophilic moiety of the DMG as a function of the group, temperature, and steric effects (anionic *ortho*-Fries rearrangement, **4.19a-e→4.20a-e**, Scheme 4.3).[11,12]



4.17 4.18

Scheme 4.2



4.19a-e 4.20a-e

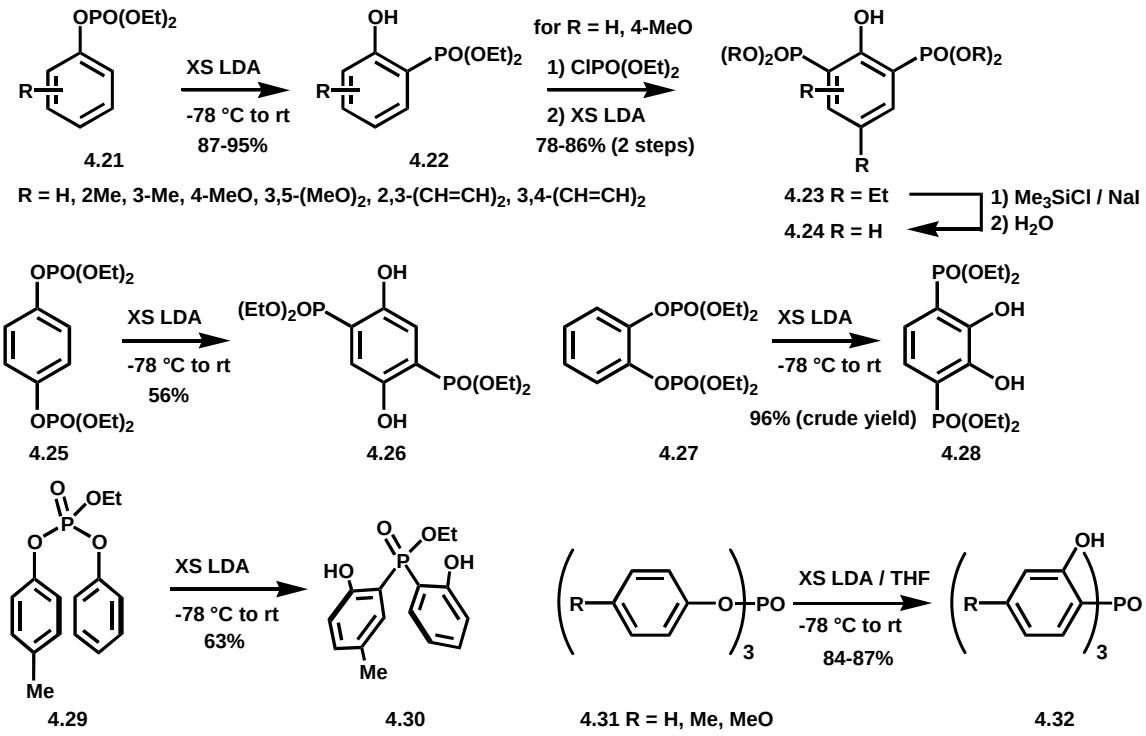
Z	
a	$CONEt_2$
b	$CONMeC(Me)_2Ph$
c	$CON(TMS)^iPr$
d	$PO(NMe_2)_2$
e	$PO(OEt)_2$

Scheme 4.3

While the latter process can be prevented through quench of **4.19a-d** with a rapid-reacting electrophile at low temperatures, its deliberate exploitation offers a convenient route to *o*-hydroxyaryl derivatives **4.20a-e**.

4.1.1 The Phosphate and Phosphorodiamidate DMGs

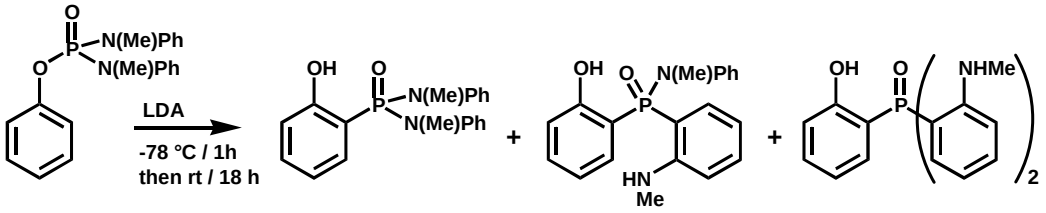
The 1,3 *O*→*C* migration of a phosphoryl group, now known as the anionic phospha-Fries or *P*-Fries rearrangement,[13] was first described by Melvin[12a] and Cambie,[12b] and was later applied by Redmore as the key step in the synthesis of *o*-hydroxyphenylphosphonic acids **4.24** (Scheme 4.4).[12c] Within the generalization of this methodology, Redmore also demonstrated the one-pot rearrangement of 1,2- and 1,4-diphosphates **4.25** and **4.27** and, conversely, the double and even triple migration of the phosphoryl group in diaryl ethylphosphate **4.29** and triarylphosphates **4.31,**[14] respectively. In the reaction of **4.29**, the absence of products with scrambled aryl substituents is indicative of the intramolecular nature of this rearrangement.[15]



Scheme 4.4

Similarly, Modro has studied these multiple migrations in phosphoramidates like $(PhO)_2P(O)N(Me)Ph$ and $PhOP(O)[N(Me)Ph]_2$ (**4.33**, Table 4.2).[16] The results of these experiments show that the *N*→*C* 1,3-migration of the phosphoryl group is remarkably slower than the more common *O*→*C* migration.

Table 4.2 1,3 *N*→*O* Phosphoryl Migration

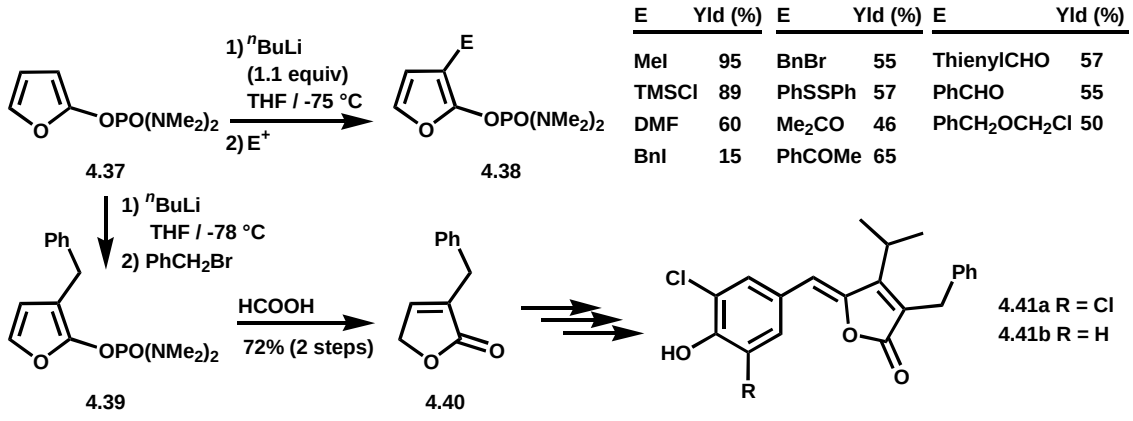


4.33

LDA (equiv)	4.34 (Yld %)	4.35 (Yld %)	4.36 (Yld %)
1.0	71	---	---
4.0	20	76	4
8.0	16	79	5

The discovery of the anionic phospha-Fries rearrangement by Cambie was a serendipitous event which arose during the attempt to hydroxylate (through D*o*M/O_2 quench) a podocarpic acid derivative *ortho* to the diethylphosphate group.[12b] Watanabe's interest in the possibility of anionic functionalization of an arylphosphate gives us the only available information on this topic. He observed that, even when generated and quenched at −105 °C (aq NH_4Cl), none of the *ortho*-lithiated intermediate **4.19e** (Scheme 4.3) escaped the 1,3-rearrangement.[12d] This result clearly suggests that no electrophilic quench could compete effectively with such a fast rearrangement, thus severely restricting the synthetic application of the $OP(O)(OEt)_2$ DMG.

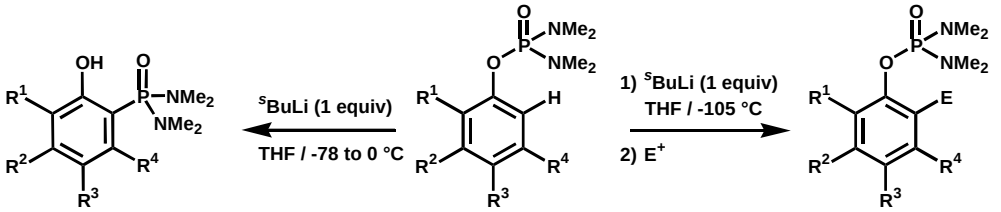
In 1986, Näsman first reported the use of the $OP(O)(NMe_2)_2$ group as a director in the *o*-metalation of **4.37** and showed its utility in the preparation of 3-substituted 2-furanones under mild hydrolytic conditions (98% HCOOH, 20 min, rt, Scheme 4.5).[17] This approach to substituted furanones was subsequently applied to the total synthesis of cytotoxic lactones nostoclides I (**4.41a**) and II (**4.41b**)[18] and a series of synthetic derivatives displaying inhibitory activity on the photosynthetic electron transport chain.[19]



Scheme 4.5

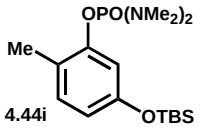
A few years later, Watanabe began exploring the potential of the $OPO(NMe_2)_2$ group as a DMG in the *ortho*-metalation of the phenyl ring. It became immediately evident that **4.19d** (Scheme 4.3) was not as stable as Näsman's furan counterpart. In fact, upon metalation and quench (aq NH_4Cl, −78 °C), **4.19d** was found to rearrange to the 2'-hydroxyarylphosphonic diamide **4.20d** in 42% yield; however, the protonated **4.19d** was completely recovered if the same sequence was repeated at −105 °C. This result was not due to lack of metalation but, rather, to the suppression of the anionic *P*-*o*-Fries rearrangement. Watanabe began a thorough generalization of the D*o*M reaction of **4.42** followed by both 1,3 phosphoryl migration (**4.43**) and electrophilic quench with a wide array of eletrophiles (**4.44**, Table 4.3).[12d]

Table 4.3 Generalization of the D*o*M of Aryl Phosphorodiamidate 4.42



4.43a-h 4.42a-i 4.44a-i-E

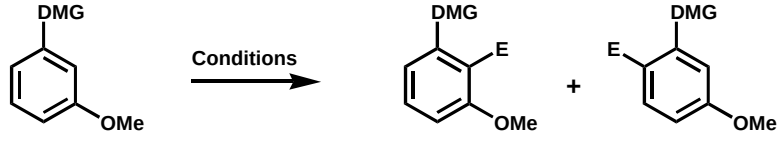
Entry	4.43a-h	(Yld %)	R^1	R^2	R^3	R^4	4.44a-i-E, E (Yld %)
1	a	80	H	H	H	H	TMS (79), PhS (64), MeCH(OH) (67) *p*-$MeOC_6H_4CH(OH)$ (67), $Ph_2C(OH)$ (72) *p*-$NO_2C_6H_4CH(OH)$ (57), Me (87), *p*-$MeOC_6H_4CO$ (94), PhMeCH(OH) (64)
2	b	80	OMe				Me (87)
3	c	90			OMe		$Ph_2C(OH)$ (58), Me (91), *p*-$MeOC_6H_4CH(OH)$ (51)
4	d	90				OMe	Me (75)
5	e	95		OMe		OMe	*p*-$MeOC_6H_4CH(OH)$ (57), Me (93)
6	f	92	$(CH{=}CH)_2$		OMe		Me (95)
7	g	90	$(CH{=}CH)_2$				Me (87)
8	h	79			$CONEt_2$		Me (94)
9	i	---				OTBS	Me (65)



4.44i

The highly selective in-between-DMGs metalation of a *m*-MeO phenyl phosphorodiamidate (**4.43d** ← **4.42d** → **4.44d**) is a clear evidence of the effective synergism between the $OPO(NMe_2)_2$ group and the weakly directing methoxy group. In this respect, the $OPO(NMe_2)_2$ group resembles the OMOM[20] and the $CONEt_2$,[21] but not the carbamate group which generates a 3:1 mixture of 1,2,3- and 1,2,4-trisubstituted products (Table 4.4) although with the caveat that a slowly reacting electrophile, CO_2 was used.[11a] The silylated product **4.44i** (entry 9) represents an exception to this trend and can be rationalized by the significant steric hindrance of the TBS group (not a DMG).

Table 4.4 Synergism between the OMe group and Some Common DMGs

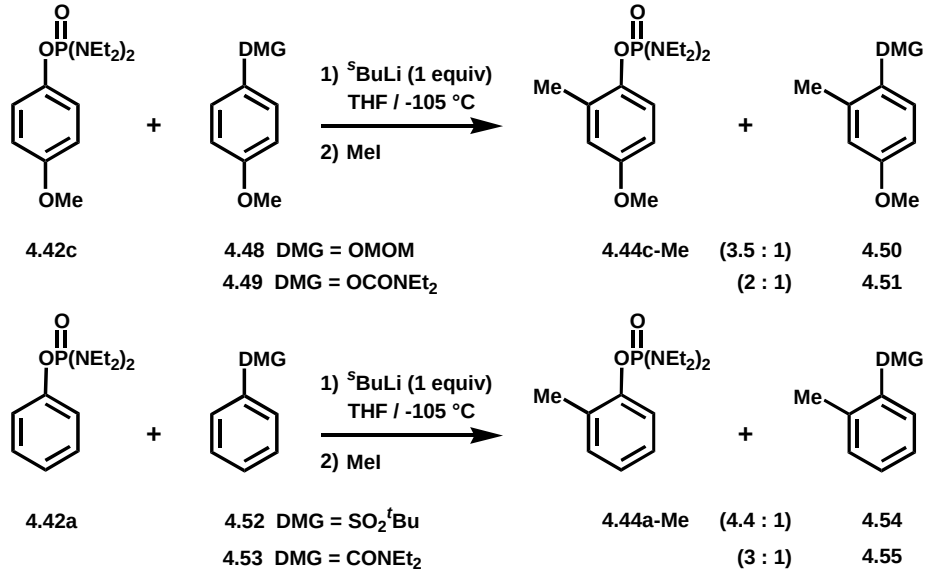


4.45 **4.46** **4.47**

DMG	Conditions	Yld % (E)	Ratio (3.46 : 3.47)
OMOM	^{t}BuLi / hexanes / 0 °C	78 (I)	97 : 3
OMOM	^{t}BuLi / Et_2O / 0 °C	95 (I)	59 : 41
OMOM	^{t}BuLi / TMEDA / Et_2O / -78 °C	93 (I)	95 : 5
$OCONEt_2$	^{s}BuLi / TMEDA / THF / -78 °C	83 (CO_2H)	76 : 24
$CONEt_2$	^{s}BuLi / TMEDA / THF / -78 °C	88 (D, 90% d_1)	>95 : <5
$OPO(NMe_2)_2$	^{s}BuLi / THF / -105 °C	75 (Me)	>95 : <5
$OPO(NMe_2)_2$	^{s}BuLi / THF / -105 °C	90 (*o*-Fries)	>95 : <5

Watanabe also assessed the directing power of the $OPO(NMe_2)_2$ group through intermolecular and intramolecular competition studies. When 1:1 mixtures of **4.42c** and **4.48** were allowed to compete for 1 equivalent of ^{s}BuLi followed by MeI quench, a 3.5:1 ratio of the products **4.44c-Me** and **4.50** was obtained, demonstrating that the phosphorodiamidate group is a stronger DMG than the OMOM group (Scheme 4.6).[12d] Under the same conditions, the $OP(O)(NMe_2)_2$ group was estimated to be threefold

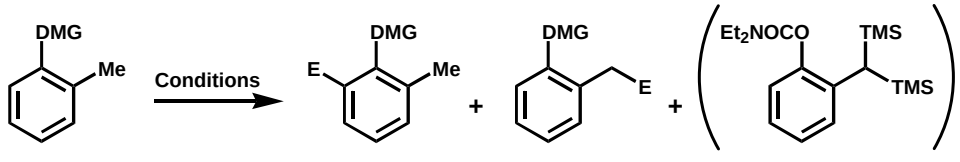
stronger than the $CONEt_2$ group, fourfold stronger than the $SO_2{}^tBu$ group (4.4 :1 ratio) and even twice as strong as the powerful $OCONEt_2$.



Scheme 4.6

The high yields in the *ortho*-methylation reaction of **4.42c** and **4.42h** (91 and 94% respectively, Table 4.3) is circumstantial confirmation that, as observed in the intermolecular competition experiments, the directing power of the phosphorodiamidate group surpasses that of the methoxy and the diethyl amide groups. Watanabe also studied the lateral metalation of variously substituted *o*-tolylphosphorodiamidate **4.44a-Me** and found that the $OPO(NMe_2)_2$ group is the strongest lateral director when compared with other *O*-based DMGs (Table 4.5).[22] This behaviour complements the metalation chemistry of MOM-derived *ortho*-cresol which undergoes exclusive *ortho*-metalation when treated with ^{t}BuLi at 0 °C. On the other hand, the metalation of *ortho*-cresyl-*O*-carbamate **4.56** (DMG = $OCONEt_2$) occurs with *ortho* or lateral selectivity as a function of experimental conditions.[11a]

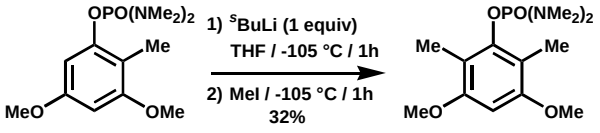
Table 4.5 Directed *ortho vs* Lateral Metalation for Some *O*-Based DMGs



4.56 4.57 4.58 4.59

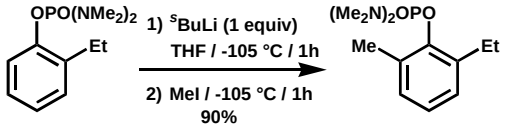
DMG	Conditions	Yld % (E)	Ratio (4.57 : 4.58)
OMe	^{n}BuLi / TMEDA / cyclohexane / rt / 10 h	72 (CO_2H)	72 : 25
OMe	^{t}BuLi / cyclohexane-pentane / reflux / 10 h	81 (CO_2H)	42 : 58
OMe	^{n}BuLi / cyclohexame / reflux / 10 h	57 (CO_2H)	33 : 67
OMOM	^{t}BuLi / hexane/ 0 °C / 1 h	87 (I)	99 : nil
$OCONEt_2$	^{s}BuLi / TMEDA / THF / -78 °C / 1 h	? (TMS)	67 : 33
$OCONEt_2$	LDA / THF / -78 °C/ 1 h	78 (TMS)	85 : 15 (3.57 : 3.58)
$OPO(NMe_2)_2$	^{s}BuLi / THF / -105 °C / 1 h	81 (Me)	nil : 99

It is interesting, however, that the metalation of **4.44e-Me** does not occur, as expected, at the lateral position (Scheme 4.7).[22b] While none of the ethyl substituted product was observed, the reaction gave only 32% of the *ortho*-methylated product **4.60**. It appears that the directing power of the phosphorodiamidate and the methoxy groups do not combine towards the lateral metalation as effectively as in the *ortho*-metalation. The diminished acidity of the benzylic hydrogens may be due to the presence of the electron donating *ortho* and *para* methoxy groups.[23] Similarly, the inductive effect of the benzylic substituent may play a critical role in preventing the lateral metalation of **4.61** (Scheme 4.8).[22b]



4.44e-Me 4.60

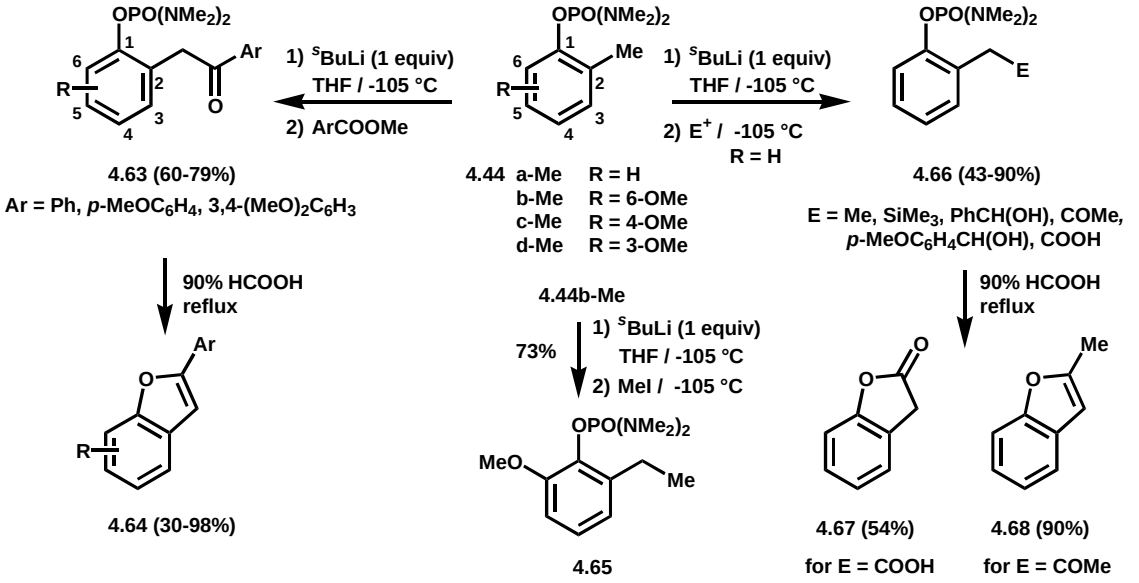
Scheme 4.7



4.61 4.62

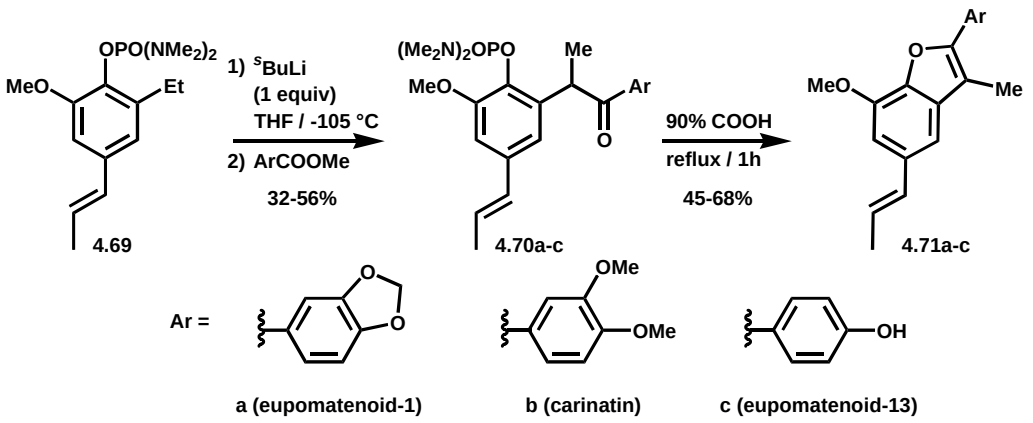
Scheme 4.8

In particular, the lateral metalation of **4.44a-d-Me** followed by quench with methyl benzoates was exploited for the synthesis of methoxy-substituted 2-arylbenzofurans **4.64** (Scheme 4.9). These were obtained through one-pot hydrolytic cleavage of the phosphorodiamidate **4.63** and subsequent intramolecular condensation. Similarly, **4.67** and **4.68** were obtained using the same refluxing formic acid conditions from some of the products **4.66**.



Scheme 4.9

In the total synthesis of three naturally occurring neolignans (carinatin, eupomatenoid-1 and -13, **4.71a-c**, respectively) this approach to the benzofuran frame requires lateral metalation of **4.69** which, due to the reduced acidity of the benzylic hydrogens (compare with **4.44b-Me→4.65**, Scheme 4.9), suffered from low yields of products **4.70a-c** (Scheme 4.10).



Scheme 4.10

The anionic chemistry of phosphorodiamidates did not find a practical application until, in 1998, Buono began using the *P-ortho*-Fries rearrangement for the synthesis of new chiral *o*-hydroxylaryl phosphoric diamides **4.72-4.75** which he applied as ligands in the enantioselective addition of diethylzinc to benzaldehyde (Fig. 4.1).[24]

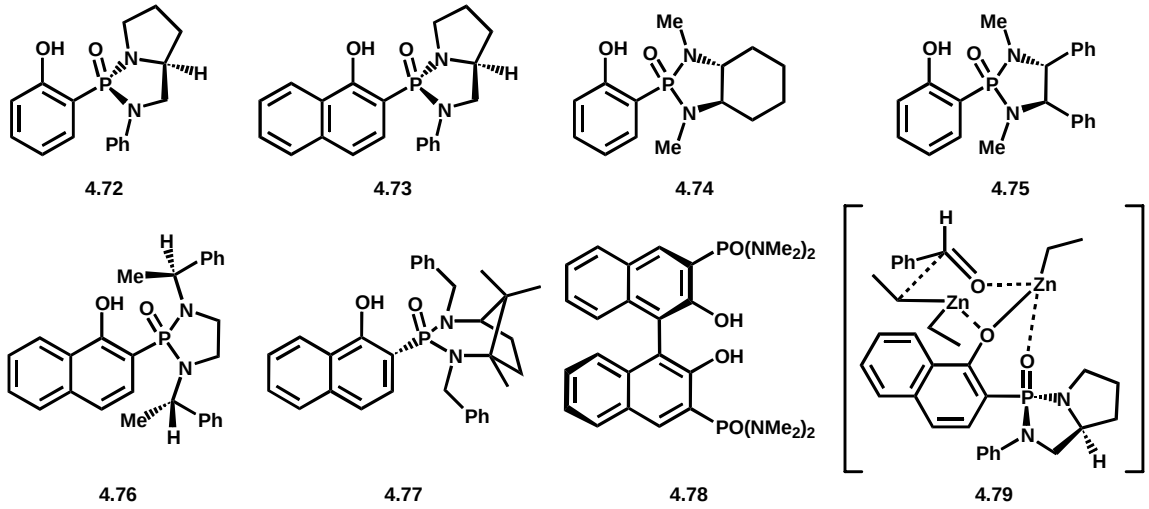
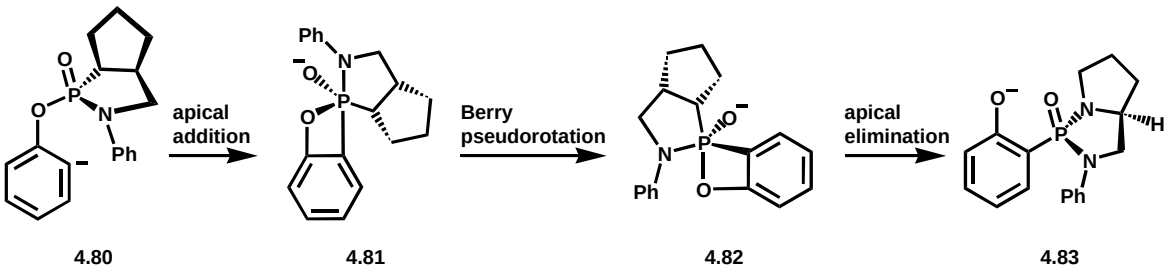


Figure 4.1 *P*-Ligands Obtained from the *P*-Fries Rearrangement of Aryl Phosphorodiamidates

The good performance of these catalysts depends indeed on the molecular imprint of the anionic *P*-*ortho*-Fries rearrangement – that is, on the presence and mutual proximity of both a free hydroxyl group and a phosphoryl group. When chelated by these two groups, Et_2Zn acts as a Lewis acid in the activation of the electrophile, while the nucleophile is activated by the phenoxide moiety (**4.79**).[25] Thanks to this web of interactions, no $Ti(O^iPr)_4$ is required for the selective $ZnEt_2$ addition, although the silylcyanation of aromatic aldehydes, as described by Zhou with **4.76** and **4.77**, still requires the *in situ* formation of a titanium complex.[26] Finally, Ishihara has recently launched a second generation of *O*,*O*-bifunctional ligands characterized by axial chirality whose synthesis is again based on the anionic phospha-Fries rearrangement of a 2,2'-phosphorylated BINOL.[27] In particular, **4.78** gives very high yields and ees (generally >90% and up to > 99%) in the dialkylzinc addition to aromatic aldehydes. It is noteworthy that, in all cases described, the 1,3 *O*→*C* rearrangement of all starting arylphosphorodiamidates invariably occurs with retention of configuration at the phosphorus atom. This feature has been rationalized with a mechanism proceeding through a trigonal bipyramidal (TBP) intermediate (Scheme 4.11). For associative processes involving strong nucleophiles, the formation of a TBP intermediate is generally assumed in which the nucleophile occupies the apical position.[28] Thus, in **4.81**, the oxaphosphetane and the diazaphospholane rings adopt an axial-equatorial position while the negatively charged oxygen occupies an equatorial position. A Berry pseudorotation[29] in which the charged oxygen is the pivot bond, reorganizes the TBP so that the more apicophilic oxygen atom of the oxaphosphetane adopts the axial position (**4.82**). An apical elimination opens the

oxaphosphetane ring and generates a product with retention of configuration at the phosphorus atom (**4.83**).



Scheme 4.11

Consistent with Watanabe's observations (Table 4.4), this rearrangement also occurs with high regioselectivity. Thus, under the combined directing effects of the diazaphospholidine oxide and the methoxy, chloro, or fluoro groups, only the phosphonamides **4.84** were obtained from the corresponding phosphorodiamidates (Fig. 4.2).[24a] The observed formation of **4.85** and **4.86** in a 3:1 mixture is the result of an unusually indecisive rearrangement whereas the selective formation of **4.87** is undoubtedly due to the steric hindrance of the *t*butyl group.[24a]

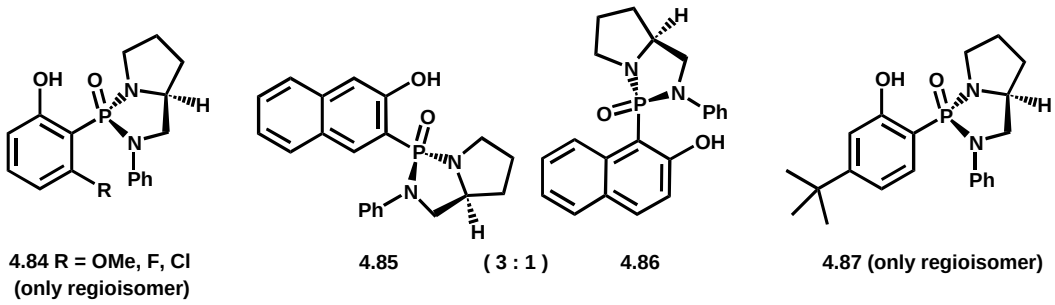
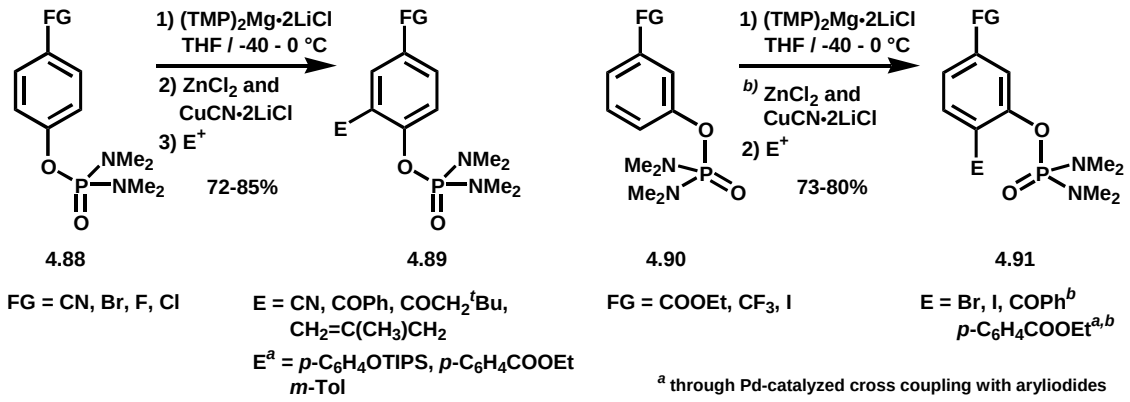


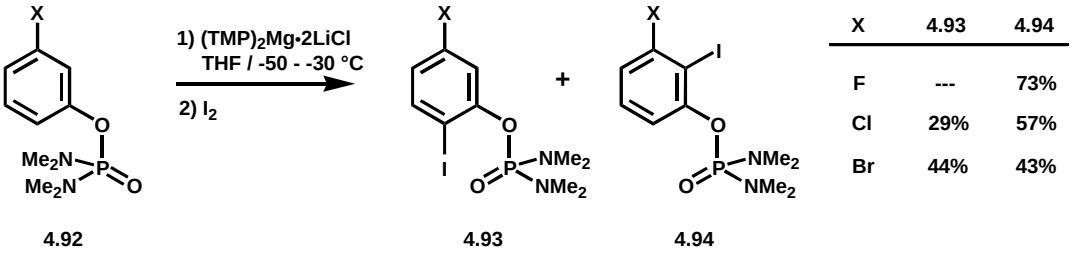
Figure. 4.2 Products of Regioselective Phospha-Fries Rearrangement

It was not until 18 years after Watanabe's work[12d,22] that the external quench of an *o*-lithiated arylphopshorodiamidate was revisited. Within a study on the scope of the mixed

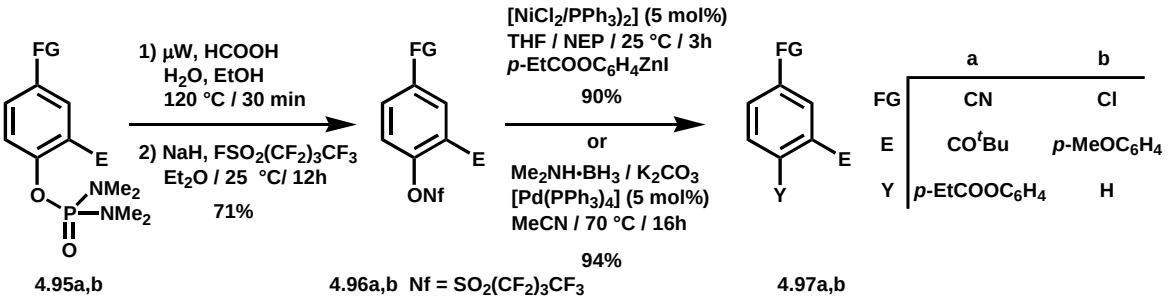
Li/Mg base $(TMP)_2Mg{\bullet}LiCl$, Knochel demonstrated the use of the sensitive COOEt, COO^iPr, COO^tBu and CN groups as DMGs in the *ortho*-magnesiation of the benzene and pyridine rings under conditions not involving very low temperatures (–40 - 0 °C).[30] Particularly, a full paper was dedicated to showcasing the potential of this new base in the *o*-metalation of arylphosphorodiamidates with particular emphasis on its application in the synthesis of unusually 1,2,4-trisubstituted arenes **4.89** and **4.91** and the FG compatibility of the base (Scheme 4.12).[31] While in most examples the final products were obtained from transmetalated arylzinc intermediates by Pd-catalyzed cross coupling or quench with electrophiles, direct quench of the *ortho*–lithiated species was only shown in a few cases involving electrophiles such as $(BrCl_2C)_2$, I_2 and ^{t}BuCHO. With the exception of iodine, halogens displayed synergistic DMG effects with the $OPO(NMe_2)_2$ group leading to mixtures of 1,2,3- and 1,2,4-trisubstituted products **4.93** and **4.94** and, for X = F, solely to the 1,2,3-substituted derivative (Scheme 4.13). A synthetic sequence was also optimized that indirectly allowed the removal of the DMG. Thus, HCOOH-mediated hydrolysis of **4.95a,b** under microwave irradiation and subsequent conversion of the phenol to a nonaflate **(4.96a,b)** allowed conduit to Ni- and Pd-catalyzed Negishi cross coupling or reductive cleavage chemistry at the position which originally bore the powerful DMG (Scheme 4.14).



Scheme 4.12



Scheme 4.13

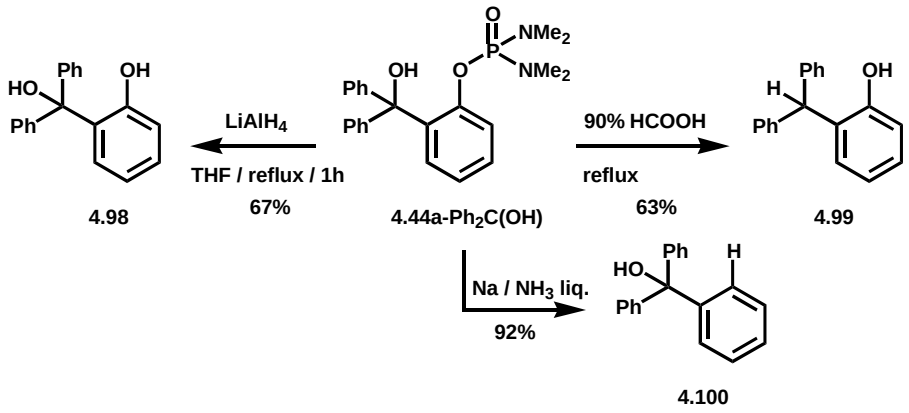


Scheme 4.14

4.2 Aims of Research

It may appear surprising that, despite its high *ortho*-directing power, the $OPO(Me_2)_2$ group has had little impact and applications in synthetic chemistry. This was most likely due to the fact that the quench of an *o*-lithiated arylphosphorodiamidate with an external

electrophile requires impractical metalation temperatures (– 105 °C) in order to prevent the facile anionic *ortho*-Fries-type rearrangement. Furthermore, the release of a synthetically useful *ortho*-substituted phenol occurs under conditions incompatible with most functional groups. For example, the reductive cleavage of the $OPO(NMe_2)_2$ group with sodium in liquid ammonia has been successfully carried out only in bare carbon skeletons for obvious reasons of FG compatibility (*e.g.*, **4.44a-Ph_2C(OH)→4.100**, Scheme 4.15).[12d,32] Unlike in Näsman's furan series,[17-19] refluxing in 90% formic acid (~ 100 °C) is required to hydrolyze **4.44a-Ph_2C(OH)** with unavoidable reduction of the tertiary alcohol to give **4.99**. Similarly, treatment with $LiAlH_4$ in boiling THF is capable of unmasking the phenolic functionality as observed for **4.98**; however, reduction of most common unsaturated groups is to be expected under these unselective conditions. For these reasons the definition of latent DMG cannot be unanimously applied to this group.

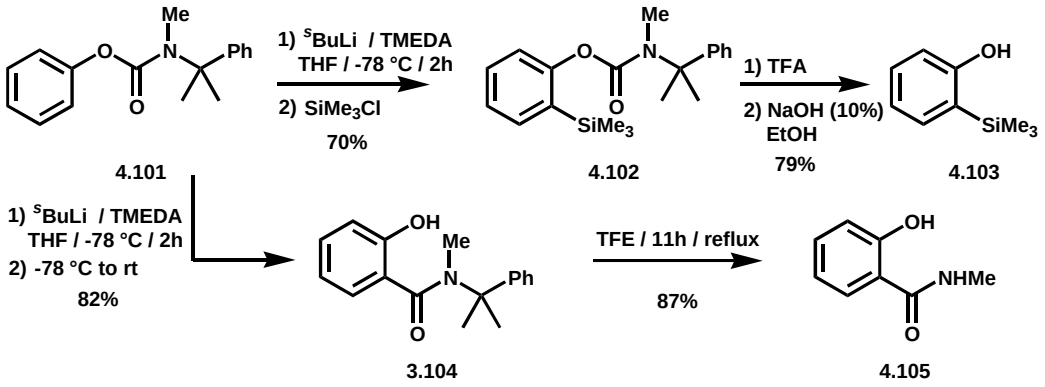


Scheme 4.15

The recent work of Knochel has begun to speak to the question of synthetic applicability for this DMG, a quality tightly linked not only to directing power but also to its chemical pliability. In view of Knochel's improvement of the experimental conditions for the

metalation and hydrolysis of arylphosphorodiamidates (CN and COOEt groups have been shown to withstand microwave irradiation at 120 °C), a rediscovery of this DMG can be anticipated.

In our group, the constant attention towards synthetic applicability of DMGs has led to work with a two-pronged strategy. On one side, fine-tuning of the DMG's structure has resulted in the design of more labile DMGs. To illustrate, the *N*-cumyl carbamate group can direct *ortho*-metalation (**4.101→4.102**) just as well as the diethyl carbamate group, but it decumylates under mild acidic conditions to unveil the modified functionalized phenol (**4.103**, Scheme 4.16). Alternatively, **4.101** may undergo anionic *ortho*-Fries rearrangement and thus be converted to a secondary amide group (**4.105**).



Scheme 4.16

On the other hand, for the stable $OCONEt_2$ group synthetic value has been added with the development and generalization of useful post-D*o*M or DreM reactions in which anchimerically assisted processes are pivotal features (Fig. 4.3).[33]

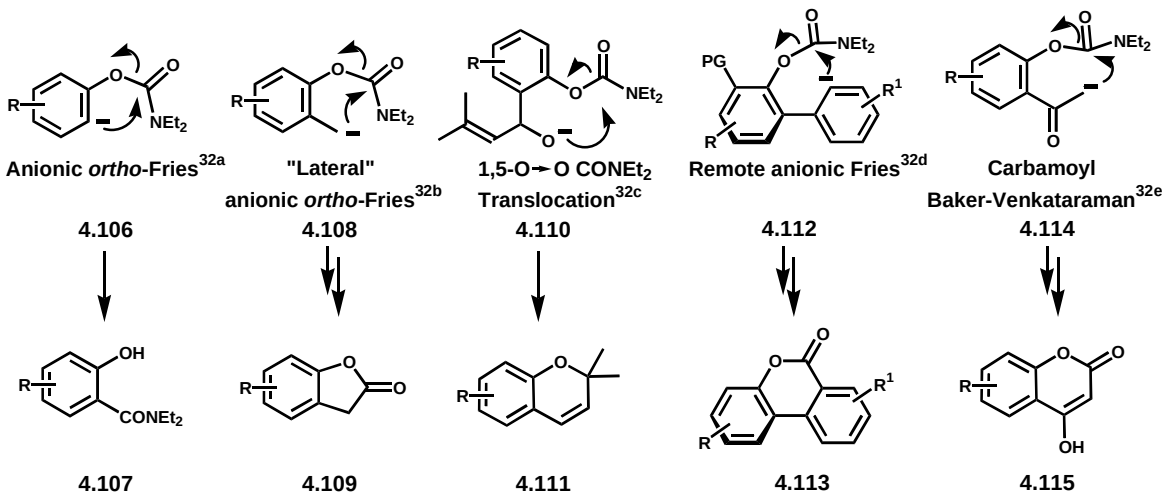


Figure 4.3 Synthetic Manipulation of the Carbamate Group through Translocation reactions

In this context, we aimed to a) design a phosphorodiamidate directing group that displays an improved stability under standard metalation conditions and b) explore synthetic applications beyond the phenol phosphorylation/D*o*M/dephosphorylation sequence for which the $OPO(NMe_2)_2$ appears unsuitable. Failures and successes towards these goals will be described.

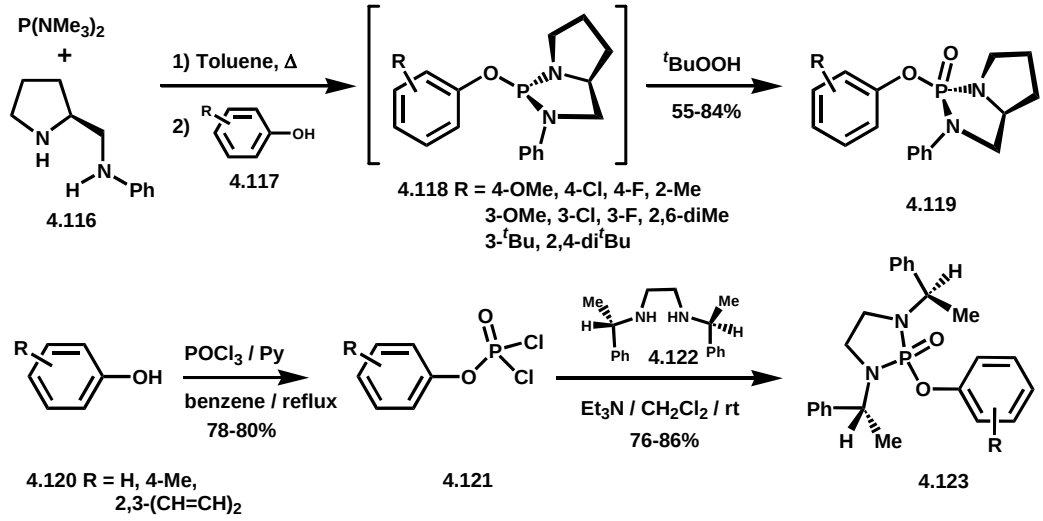
4.3 Results and Discussions

The anionic phospha-*ortho*-Fries rearrangement is a synthetically useful reaction as demonstrated by its applications in the synthesis of the Buono, Zhou and Ishihara chiral catalysts. However, bringing this process under control and diverting the *o*-lithiated intermediate towards a quench with an external electrophile requires, at least in Watanabe's approach (Table 4.3),[12d] a rather drastic and costly solution. There are at least two more approaches to this problem: a) stabilization of the *o*-metalated intermediate which Knochel has achieved using the Li/Mg mixed base

$TMP_2MgCl{\cdot}2LiCl$. This approach requires switching from the standard *o*-lithiated species to a less reactive *o*-magnesiated phosphorodiamidate, an intermediate which even at 0 °C does not undergo 1,3 migration of the phosphoryl group, and b) a parallel strategy to decelerate the phospha-Fries rearrangement by stabilization through structural modification of the reactive phosphorodiamidate moiety. Unwanted nucleophilic reactions at DMGs have been a frequent occurrence and have often been addressed by increasing their size or relying on their deactivation by *in situ* deprotonation (*e.g.*, DMG = CONHMe),[34] *in situ* reversible addition of the base (DMG = CHO/LNMP and CHO/LTMDA adducts)[35] and *in situ* electrophilic quench (DMG = $COCH_2{}^tBu$, CN).[36] Within the first approach, Beak's establishment of the $CONEt_2$ and $CON{}^iPr_2$ groups as synthetically useful DMGs[37] was stimulated by Hauser's finding that ^{n}BuLi adds to $PhCONMe_2$ to form valerophenone (70%). Other bulky amide DMGs successfully tested with ^{s}BuLi and ^{t}BuLi are $CON(Et)CH_2CH_2NEt_2$,[38] $CON(^iPr)CH_2SiMe_3$,[39] $CON(Me)CH(SiMe_3)_2$[40] and, to a lesser extent, the piperidino amide group. The self condensation of diethyl pyridinecarboxamides upon metalation with LDA or ^{s}BuLi offers another facet of this problem which has been usually tackled with the use of the more hindered diisopropylamide homologues (Section 1.4). Based on these precedents, we hypothesized that a tetra*ethyl*phosphorodiamidate group ($OPO(NEt_2)_2$) would be less prone to undergo 1,3 migration and allow the introduction of an external electrophile at standard metalation temperatures (−78 °C).

4.3.1 The D*o*M of Phenyl *N*,*N*,*N*',*N*'-Tetraethylphosphorodiamidates 4.126a,b

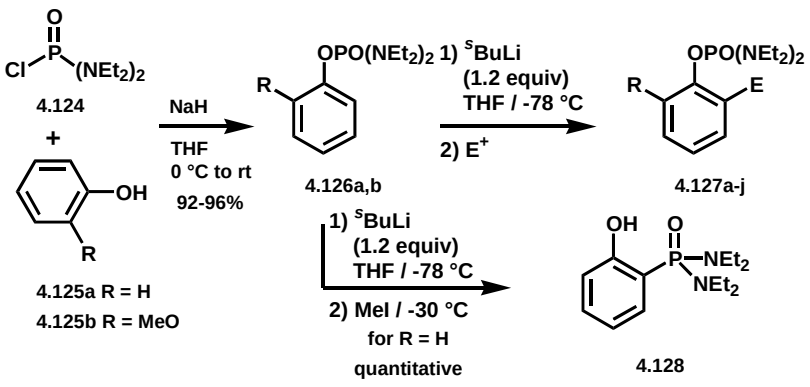
The reported synthesis of arylphosphorodiamidates involves three similar approaches. Several ring-substituted chiral arylphosphorodiamidates such as **4.119** have been synthesized through an exchange reaction between the chirally pure pyrrolidine **4.116** and tris(dimethylamino)phosphane, followed by addition of the appropriate phenol (**4.117**, Scheme 4.17).[24a,c,d] The subsequent ^{t}BuOOH oxidation of the crude **4.118** is generally highly stereoselective and avoids the difficult separation of diastereomeric mixtures of **4.119**. Alternatively, as in the synthesis of **4.123**, the chiral amine **4.122** may be directly combined with a substituted aryl phosphorodichloridate (**4.121),**[41] and the separation of the diastereomeric products is addressed at this point or at a later stage of their structural modification.[24b,26c]



Scheme 4.17

The most undemanding approach, well suited for simple achiral phosphorodiamidates, is the reaction of a substituted phenol with a tetraalkylphosphorodiamidic chloride ($ClPO(NR_2)_2$), commercially available for R = Me, Et.[42] Thus, using this method, **4.126a** was obtained in 96% yield and was subjected to metalation to test its ability to generate a

persistent *o*-lithiated species at −78 °C (Scheme 4.18). In keeping with Watanabe's protocol, deprotonation was effected with ^{s}BuLi for 1 h and, to our delight, the resulting lithiated intermediate was found to intercept TMSCl in 84% to give **4.127a** without any competition from the alternative 1,3 rearrangement. The stability of the lithio-intermediate was probed further by allowing the reaction mixture to reach −30 °C prior to the addition of MeI. However, under these conditions, the lithiated intermediate was found to quantitatively rearrange to **4.128**. Thus, through a simple enhancement of bulk, the stability of Watanabe's DMG appeared to have been tuned to approximately match that of the carbamate group, which undergoes the 1,3 migration at ~ −50 °C. Generalization of this reaction was pursued in enthusiastic collaboration,[43] and led to the synthesis of several derivatives **4.127a-j** in satisfactory yields. In particular, *o*-formylation of **4.126a** with anhydrous DMF was a consistently quantitative reaction while the incomplete conversion of **4.127f** to a less polar but more readily isolable boropinacolate may, in part, explain its low isolated yield. Good yields were also obtained from the *ortho*-metalation of 2-methoxyphenylphosphorodiamidate **4.126b** to give products **4.127i,j**.

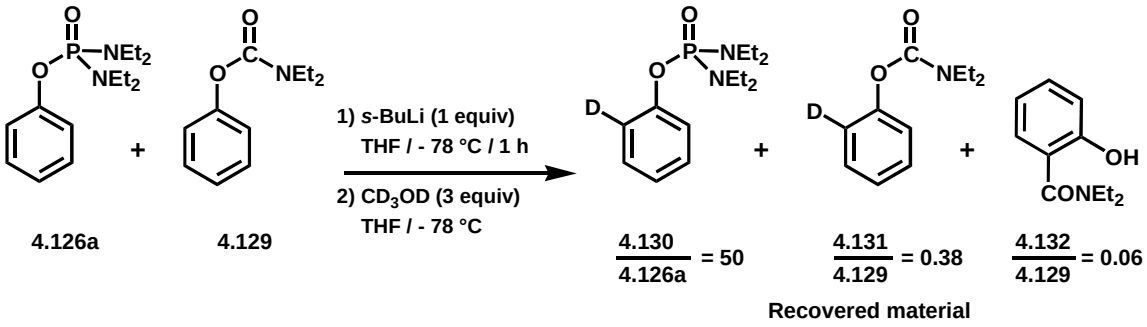


4.127	R	E	Yld (%)
a	H	TMS	84
b	H	Me	89
c	H	I	86
d	H	Br	67
e	H	CHO	quant.
f	H	$B(OH)_2$	52*
g	H	SPh	77
h	H	$CONEt_2$	61
i	MeO	Me	88
j	MeO	TMS	86

* isolated as pinacol ester

Scheme 4.18

An important question to address was whether or not the structural changes of Watanabe's $OP(O)(NMe_2)_2$ DMG to the corresponding $OP(O)(NEt_2)_2$ DMG imposed an effect on directing power. An intermolecular experiment was carried out by metalating an equimolar mixture of **4.126a** and **4.129** with only half the stoichiometric amount of ^{s}BuLi (Scheme 4.19). After stirring for 1 h at −78 °C, the reaction mixture was quenched with excess of CD_3OD, and the products were separated and analyzed to reveal that 50% of **4.126a** and 44% of **4.129** had been lithiated (the latter gave 38% of **4.131** and 6% of the *o*-Fries rearrangement product **4.132**). The outcome of these experiments implies not only that the directing power of the $OPO(NEt_2)_2$ group is comparable to that of the carbamate group, but also that the former is (at least slightly) more stable than the latter towards the *O*→*C* 1,3-migration.

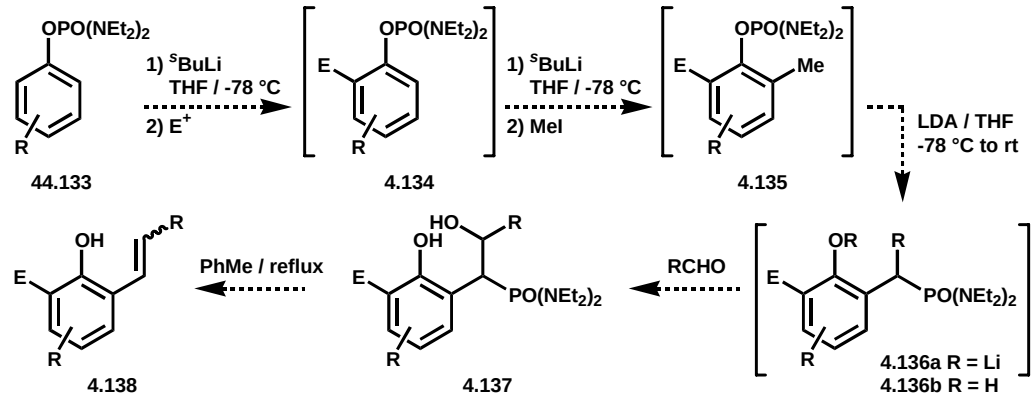


Scheme 4.19

4.3.2 Lateral Metalation of Aryl Phosphorodiamidates and Phosphates

We next explored the lateral metalation capabilities of the new $OPO(NEt_2)_2$ DMG. Watanabe has already shown the high selectivity with which *o*-tolylphosphorodiamidates undergo deprotonation and subsequent electrophilic quench at the benzylic position (Scheme 4.9). Thus, our attention focused on the possible anionic vinylogous phospha-Fries rearrangement which, by transferring the bis(diethylamino)phosphoryl group to the

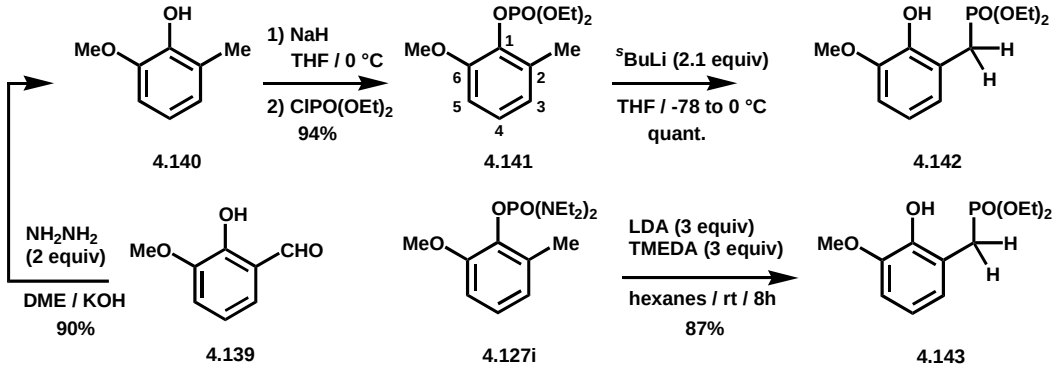
benzylic position, would furnish **4.136b**, a useful phosphonamide for the preparation of olefins **4.138** according to Corey's protocol (Scheme 4.20).[44] This would be a phosphamide analogue of the lateral metalation-carbamoyl migration of *o*-tolyl *O*-carbamates previously established in our group.[33b] Since Corey's key *β*-hydroxyphosphamides (**4.137**) are obtained by reaction of carbonyl compounds with an *α*-lithiated phosphonamide, a multi-step one-pot sequence was envisaged which, starting from a substituted phosphorodiamidate **4.133**, could conveniently lead, through a D*o*M/DreM sequence, to *β*-alkoxyphosphonamides like **4.137**.



Scheme 4.20

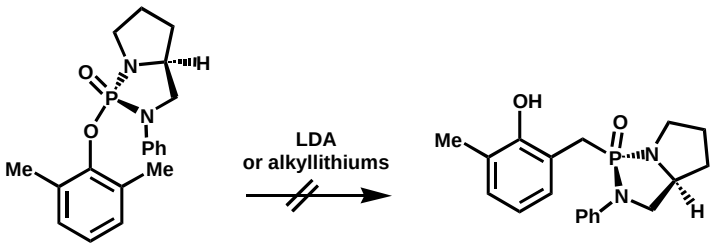
The critical step of this sequence (**4.135** → **4.136**) was tested with phosphorodiamidate **4.127i**, accessible through *o*-methylation of **4.126b** (Scheme 4.18) and, for comparison, with phosphate **4.141**, which was prepared by phosphorylation of phenol **4.140** (Scheme 4.21). In both cases, the vinylogous phospha-Fries rearrangement was attempted with 2.1 equiv of ^{s}BuLi to compensate the benzylic deprotonation of the products. Gratifyingly, both reactions gave the desired products although the migratory aptitude of the two DMGs, as seen in the instantaneous *P*-Fries rearrangement of phenyl phosphate **4.19e** (Scheme 4.3) and in the slower rearrangement of phosphorodiamidate **4.126a** (Scheme

4.18), remain strikingly different. In particular, *o*-tolylphosphate **4.141** underwent 1,4 *O*→*C* phosphoryl migration smoothly and in quantitative yield at negative temperature values to give **4.142** as unequivocally shown by the disappearance of the singlet at 3.85 ppm (C_2-CH_3) and the appearance of a signal at 3.23 ppm (Ar-CH_2) split into a doublet by the neighbouring phosphorus atom ($^2J_{P\text{-}H}$ = 21.3 Hz). The clean rearrangement of **4.141** to **4.142** is interesting as it provides a useful Horner-Wadsworth-Emmons intermediate; however, its scope is limited by the inability of the phosphate group to direct the introduction of the obligatory substituent at the C_6 position or the methylation at the C_2 position. In contrast, under the same ^{s}BuLi conditions, the corresponding phosphorodiamidate **4.127i** reacted sluggishly at rt and even upon heating to 60 °C despite its quantitative lateral metalation demonstrated by a CD_3OD quench experiment at -78 °C. However, under the unusual conditions provided by a mixture of LDA/TMEDA (3 equiv) in hexanes **4.127i** underwent lateral phosphoryl migration to **4.143** in nearly complete conversion and 87% isolated yield.



Scheme 4.21

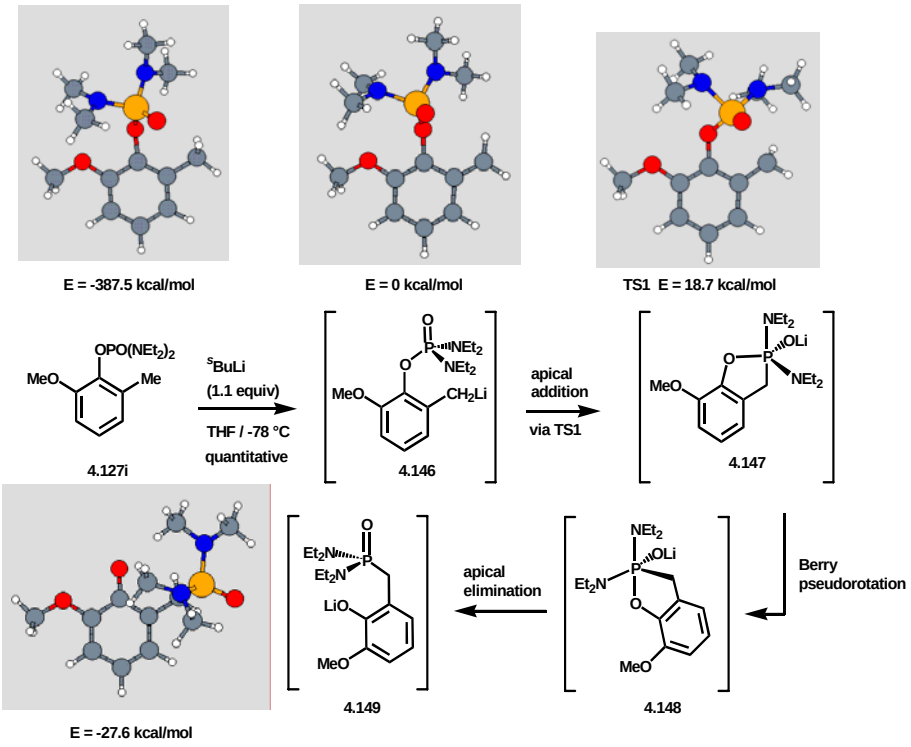
A similar result has been reported by Buono on the chiral phosphorodiamidate **4.144** (Scheme 4.22); however, in this case, no proof of benzylic deprotonation could be obtained from the addition of electrophiles to the reaction mixture.[24c]



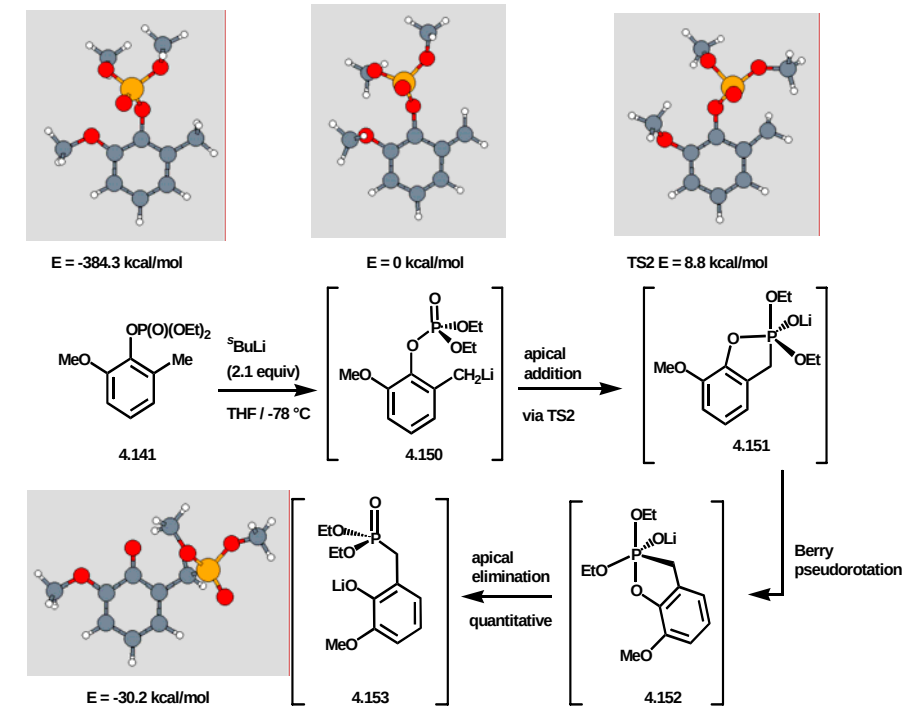
4.144 4.145

Scheme 4.22

In our case, the facile deprotonation of **4.127i** at low temperatures together with its slow rearrangement to **4.143** point at the formation, Berry pseudorotation or apical elimination of the TBP intermediates **4.147** and **4.148** as the slow steps of this reaction (Scheme 4.23). The fact that phosphate **4.141** undergoes rapid *P*-Fries rearrangement at temperatures between –78 and 0 °C suggests a non negligible difference in the energy barrier which **4.141** and its slow-rearranging analogue **4.127i** must overcome in this process. DFT calculations for the simplified $OP(O)(OMe)_2$ and $OP(O)P(NMe_2)_2$ DMGs have indeed shown that, while the two processes display similar thermodynamics, the energy barrier to the addition product **4.147** is ~10 kcal/mol higher than for the formation of the corresponding intermediate **4.151** (E_{TS1} = 18.7 kcal/mol and E_{TS2} = 8.8 kcal.mol, Schemes 4.23 and 4.24).[45]



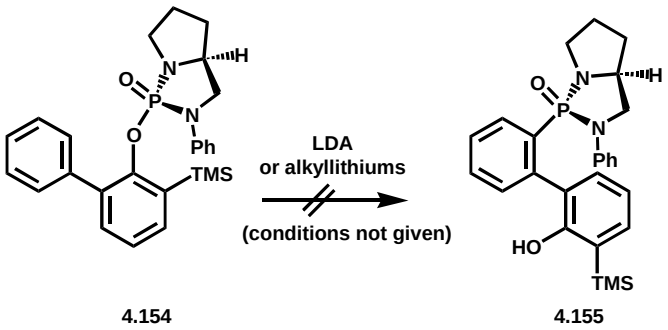
Scheme 4.23



Scheme 4.24

4.3.3 Directed remote Metalation (DreM) of Biaryl 2-phosphorodiamidates

Another post-D*o*M reaction through which the $CONEt_2$ and the $OCONEt_2$ groups have been conveniently manipulated while actively participating in the construction of natural product targets and biologically relevant skeletons, is the DreM reaction.[46] As is the case for the lateral anionic phospha-Fries rearrangement, the directed remote metalation has not been described for the phosphate and the phosphorodiamidate groups. In fact, Buono attempted to effect this reaction on the *ortho*-silylated chiral phosphorodiamidate **4.154** (not obtained by D*o*M of the corresponding desilylated precursor, Scheme 4.25). However, the lack of any reaction upon exposure of **4.154** to LDA (or LDA/E^+) led him to suggest that the diazaphospholidine oxide group does not favour a complex-induced proximity effect (CIPE).

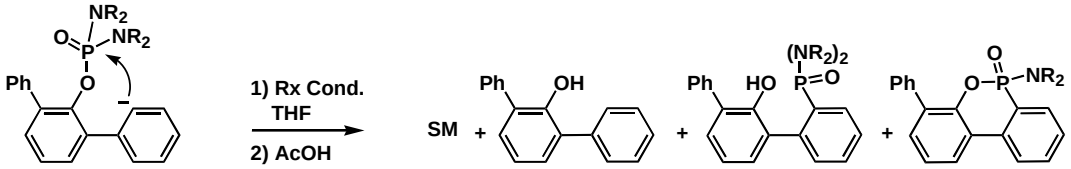


Scheme 4.25

Preliminary experiments to establish the feasibility of this reaction for phosphorodiamidates were carried out by Zumbansen[47] on the terphenyl phosphorodiamidate **4.156a**, chosen for its simple synthesis from commercially available materials and the better migratory aptitude of this DMG compared to the $OP(O)(NEt_2)_2$ group (Table 4.6). Analysis of the product mixtures obtained with different bases,

metalation temperatures and times showed that this process can indeed occur although it requires quite harsh conditions. LiTMP was found to trigger the desired 1,5 *O*→*C* migration to **4.158a** upon prolonged reaction of **4.156a** at rt (entry 1). Due to the high polarity of **4.158a**, an acidic work up was applied that allowed the isolation of the arylphosphonamide **4.159a** in low yield. The yields of the reaction improved remarkably when the lithium amide was replaced by an alkyllithium, especially when used in excess. Thus, reaction of **4.156a** with 1.4 equiv of ^{n}BuLi or ^{s}BuLi gave ~ 54% of **4.159a**, which increased to 79% when 1.6 equiv of ^{t}BuLi was used (entries 2-6). Zumbansen also tested the DreM-anionic phospha-Fries rearrangement on the tetraethyl phosphorodiamidate **4.156b** and, somewhat expectedly, found that the more hindered DMG showed a lower migratory aptitude (compare entries 4 and 7) and that, upon acidic work up of the reaction mixture, the rearranged product **4.158b** did not undergo cyclization to the corresponding phosphonic derivative **4.159b**.

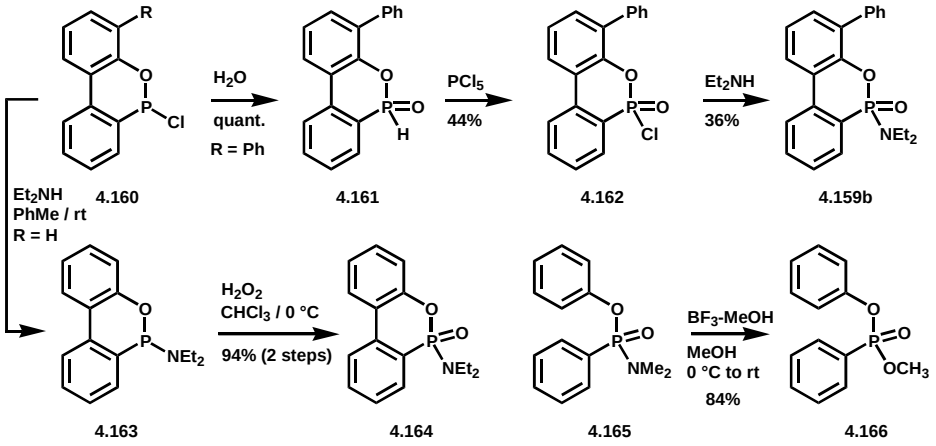
Table 4.6 *P*-DreM of Terphenyl Phosphorodiamidates 4.156a,b



4.156a R = Me, 4.156b R = Et | 4.157 | 4.158a R = Me, 4.158b R = Et | 4.159a R = Me, 4.159b R = Et

Entry	R	Reaction Conditions	SM	A	Yld, %	B	C
1	Me	LiTMP (1.2 equiv) / 1h -10 °C / 12 h at rt	11	37		---	34
2	Me	^{n}BuLi (1.4 equiv) / 1h -78 °C / 12 h at rt	16	21		---	52
3	Me	^{s}BuLi (1.4 equiv) / 2h -78 °C / 12 h at rt	15	16		---	57
4	Me	^{t}BuLi (1.2 equiv) / 1h -78 °C / 5' at rt	22	ND		---	49
5	Me	^{t}BuLi (1.6 equiv) / 1h -78 °C / 4h at rt	---	ND		---	77
6	Me	^{t}BuLi (1.6 equiv) / 1h -78 °C / 8h at rt	---	ND		---	79
7	Et	^{t}BuLi (1.2 equiv) / 1h -78 °C / 5' at rt	58	ND		32	---

Phosphonamides structurally related to **4.158** and **4.159** are generally known end products used as flame retardants.[48] **4.159b** has been synthesized from the corresponding chloride **4.160** (R= Ph) in low overall yields (Scheme 4.26).[49a] Alternatively, the oxidation of the phosphorine **4.163** afforded similar compounds by a more direct approach.[49b] Furthermore, the methanolysis of **4.165** has been shown to occur in good yield, suggesting other opportunities and applications of cyclic phosphonamides such as **4.159a** by conversion into the corresponding cyclic phosphonates.[50]

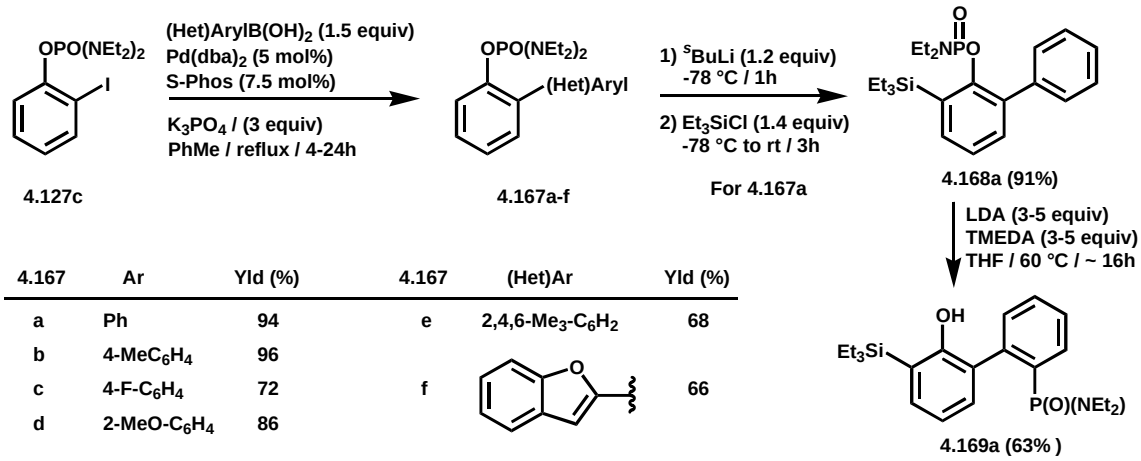


Scheme 4.26

In our group, Blackburn and Lampert have optimized the phospha-DreM reaction and have begun the exploration of its synthetic scope using several biaryl phosphorodiamidates. Compounds **4.167a-f** were obtained from an efficient Suzuki-Miyaura reaction of **4.127c** with a series of (het)aryl boronic acids (Table 4.7).[51] Upon the obligatory *ortho*-silylation, compounds **4.167a-f** appear promising substrates for the anionic *P*-DreM reaction. For instance, **4.167a** was silylated in 91% yield to phosphonamide **4.168a** which, albeit under drastic conditions (LDA/TMEDA, 3-5 equiv at 65 °C), underwent *P*-DreM in 63%. In particular, mono- or bis-methylated products

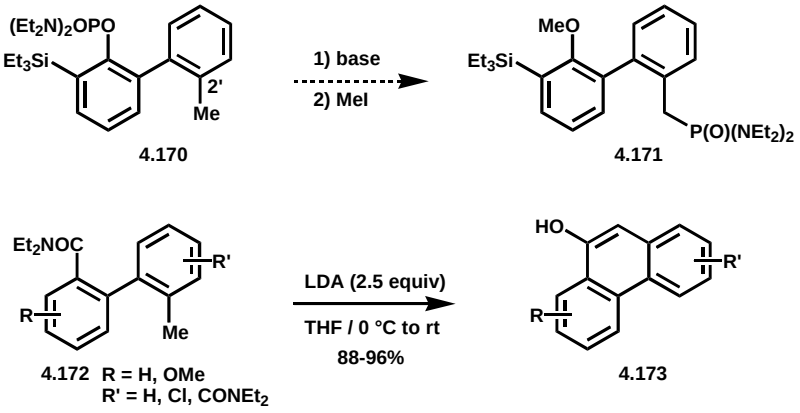
such as **4.167e** offer the opportunity for yet another variation of the phospha-DreM reaction.

Table 4.7 Suzuki-Miyaura Cross Coupling of *o*-Iodo Phosphorodiamidate 4.127c



4.167	Ar	Yld (%)	4.167	(Het)Ar	Yld (%)
a	Ph	94	e	2,4,6-Me_3-C_6H_2	68
b	4-MeC_6H_4	96			
c	4-F-C_6H_4	72	f		66
d	2-MeO-C_6H_4	86			

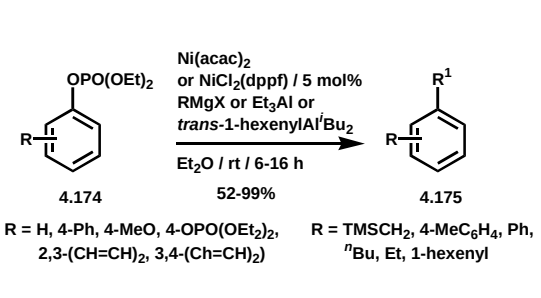
The deprotonation of the vinylogously acidic 2'-methyl hydrogen in **4.170** (Scheme 4.27) is worth testing as it may result in the translocation of the phosphoryl group to furnish the phosphamide **4.171**, a synthetically useful substrate in the Corey methodology towards olefins. In fact, Fu and Snieckus's curiosity concerning the original carbamide version of this reaction was generously rewarded with high yields of phenanthrols (**4.172** → **4.173**).



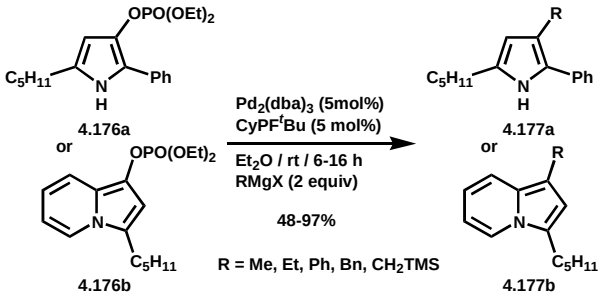
Scheme 4.27

4.3.4 Cross Coupling of Arylphosphorodiamidates

Often, the synthetic opportunities offered by a DMG need not end with the regioselective modification of the *ortho*-position(s). Resourceful heteroatom-based DMGs such as the carbamate, thiocarbamate,[52] sulfamate and sulfonamide[53] groups have granted further synthetic possibilities in that they can be removed or replaced through transition metal-catalyzed reactions. Following this strategy, it was our intention to probe the potential of the $OPO(NEt_2)_2$ group as a leaving group (LG) in cross coupling reactions. In the absence of a precedent, a screening of potential reaction conditions was based on the known coupling of the $OPO(OR)_2$ group. The only known cross coupling of aryl phosphates was developed by Kumada and involves the use of aluminium or Grignard reagents as nucleophiles under Ni catalysis (Scheme 4.28).[54] A Pd-catalyzed variation of this protocol has been recently applied to the coupling of heteroaryl phosphates with Grignard reagents (Scheme 4.29).[55] On the other hand, vinyl phosphates have been coupled under Kumada,[56] Stille,[57] Suzuki,[58] and Negishi conditions,[59,58c] and these reactions are now viable alternatives to the expensive triflate and nonaflate counterparts.



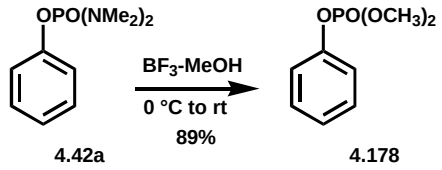
Scheme 4.28



Scheme 4.29

Furthermore, the Suzuki coupling of an alkenyl phosphate has been used successfully to connect two large precursors in the total synthesis of marine polycyclic ether (-)

gambierol.[60] Interestingly, a few examples of the Pd-catalyzed reductive cleavage of the diphenyl phosphate group have been reported.[61] Unfortunately, due to their rapid 1,3 *O→C* migration, diethyl aryl phosphates cannot be functionalized *via* D*o*M to provide *ortho*-substituted derivatives of value for cross coupling or reductive cleavage chemistry. The indirect approach chosen by Knochel for the removal of $OPO(NMe_2)_2$ group upon completion of D*o*M chemistry (hydrolysis of the DMG and formation of the nonaflate) suggests that this DMG suffers the opposite limitations (facile D*o*M, difficult cross coupling). Another indirect approach may be based on the methanolysis of aryl phosphorodiamidates which, albeit carried out under strong Lewis acid conditions, has been demonstrated to occur in good yield in limited cases (Scheme 4.30).

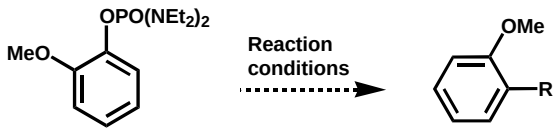


Scheme 4.30

It was recognized that the direct cross coupling of the $OPO(NEt_2)_2$ group would allow drastic widening of its synthetic potential and its applications. To date, heteroatom-based DMGs have only been cross coupled or reduced under Ni catalysis and, naturally, this was our starting point.[6,7,52,53] $Ni(acac)_2$ and IMesNiCpCl, which were the best catalysts for the cross coupling and/or the reduction of the diethyl- carbamate, sulfonamide and sulfamate groups (Scheme 4.1), failed to provide the *o*-substituted aryl phosphorodiamidates **4.179** using the prototype **4.126b** as starting material (Table 4.8). With these and other Ni catalysts, most of the Grignard reagent coupling partners was merely found as hydrolyzed products upon quench of the reaction mixture with NH_4Cl

(36-87%) or as homocoupled products. Phosphorodiamidate **4.126b** was mostly recovered unreacted (46-79%) and, in the few exceptions, its fate could not be reliably determined because of the complexity of the reaction mixture. Eventually an encouraging breakthrough came from the efforts of Blackburn and Frendo-Cumbo,[62] who tested the conditions recently established by Skrydstrup for the coupling of vinyl phosphates with arylboronic acids (Entry 4, Table 4.9).[63]

Table 4.8 Catalyst Screening for the Kumada-Corriu Cross Coupling of 4.126b



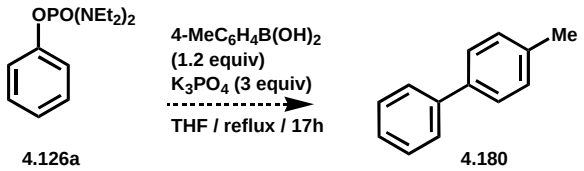
4.126b **4.179**

Catalyst (5 mol%) Ligand	RMgX (1.5 equiv)	Conditions
$Ni(acac)_2$/ dppp	PhMgBr	THF / rt / 24h
$Ni(acac)_2$	PhMgBr (3equiv)	Et_2O / rt / 15h
$NiCl_2(PPh_3)_2$	4-$MeOC_6H_4MgCl$	Et_2O / rt / 15h
	or	
IPrNi(Cp)Cl	2-MeC_6H_4MgCl	Et_2O / rt / 15h
	or	
IMesNi(Cp)Cl	$TMSCH_2MgCl$	Et_2O / rt / 15h

Frendo-Cumbo found that, although PCy_3 (generated *in situ* from the stable tetrafluoroborate salt) is beneficial in the Ni-catalyzed coupling of **4.126a** (entry 4), it loses its efficacy when used in combination with $Pd(dba)_2$ or $Ni(acac)_2$ (entries 3 and 5, respectively). Changing PCy_3 with P^tBu_3, concordantly with Skrydstrup's experience, led to worse results, while the *N*-heterocyclic carbene-based Ni catalysts (entry 6) did not catalyze the reaction at all. Finally, optimization of these promising conditions through tests in different solvents, pointed to the effect of toluene (entry 5, Table 4.10). While refluxing of the reaction mixture in toluene gave 44% of **4.180**, this yield could be

improved to 70% through microwave irradiation to 150 °C (entry 6). While these preliminary results are encouraging, it is important that the generalization of this reaction include several cases of *o*-substituted phenyl phosphorodiamidates. If an effective D*o*M-cross coupling link for the $OPO(NEt_2)_2$ group is to be established, the possible steric and electronic effects of substituents adjacent to the coupling site must be thoroughly explored and addressed through further optimization of the reaction conditions.

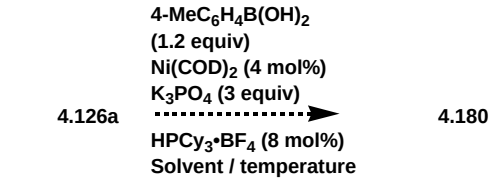
Table 4.9 Catalyst Screening for the Suzuki-Miyaura Cross Coupling of 4.126a



4.126a 4.180

Entry	Catalyst (5 mol%)	Ligand	
1	$NiCl_2$	dppf	---
2	$NI(COD)_2$	P^tBu_3 (6 mol%)	traces
3	$Pd(dba)_2$	$HPCy_3{\bullet}BF_4$ (8 mol%)	---
4	$Ni(COD)_2$ (4%)	$HPCy_3{\bullet}BF_4$ (8 mol%)	17%
5	$Ni(acac)_2$ (4%)	$HPCy_3{\bullet}BF_4$ (8 mol%)	---
6	IMesNi(Cp)Cl, IPrNi(Cp)Cl, SiMesNi(Cp)Cl	---	---

Table 4.10 Solvent Screening for the Suzuki-Miyaura Cross Coupling of 4.126a

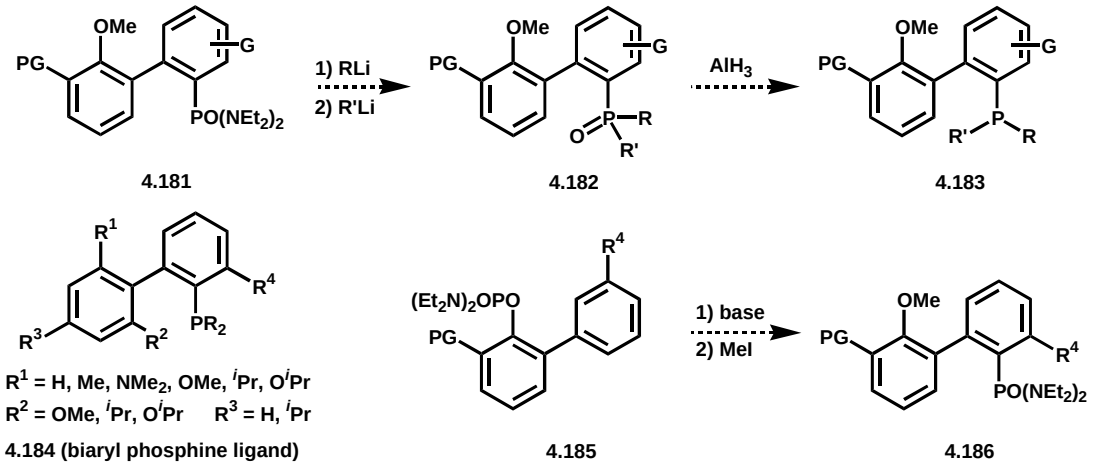


Entry	Solvent / temperature	
1	DMF / reflux / 24h	---
2	xylenes / reflux / 24h	4-7%
3	dioxane / reflux / 24h	---
4	DME / reflux / 24h	---
5	toluene / reflux / 24h	44%
6	toluene / (μW irradiation / 150 °C) / 1h	70%

4.4 Future Work

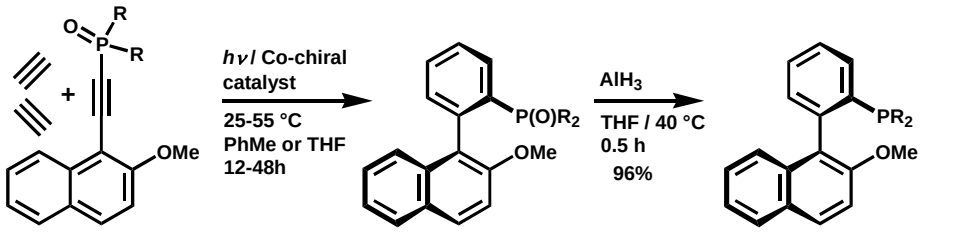
While the *ortho*-directing ability of the $OPO(NEt_2)_2$ group has been fully demonstrated, other applications of this DMG remain to be explored and generalized, a process that Blackburn has recently initiated. In context of potential utility, the *P*-DreM reaction may also offer an interesting contribution in the field of *P*-ligand synthesis. Through their stepwise reduction to phosphines **4.183** (Scheme 4.31), phosphonamides **4.181** may represent valuable intermediates towards the synthesis of biaryl phosphine ligands which are successfully used in challenging Suzuki-Miyaura cross coupling reactions. The synthetic potential of the D*o*M of aryl phosphorodiamidates would thus provide access to biaryl phosphines with unusual substitution patterns. The desirable features of a biaryl phosphine ligand have been established by Buchwald.[64] Among several advantageous characteristics, substitution of the non phosphorylated ring, especially at $C_{2'}$ and $C_{6'}$, (**4.184**, Scheme 4.31) has been found to increase the stability and, by effect of its greater

size which discourages further coordination, also the concentration of monoligated $L_1Pd(0)$, the key species in the catalytic cycle. On the phosphorylated ring, a substituent *ortho* to phosphorus (R^4) locks the conformation of the phosphine group relative to the alternate ring and increases the rate of reductive elimination. If possessing directing ability, R^4 can be predicted to facilitate a regioselective phospha-DreM reaction by synergistically combining its directing effect with that of the phosphorodiamidate DMG (**4.185** → **4.186**). Compound **4.188f**, structurally related to the DreM product **4.159a** and **4.169a** (Tables 4.9 and 4.10, respectively), have been synthesized as a member of a series of phosphorus-bearing axially chiral biaryls obtained by Co-catalyzed asymmetric cross-cyclotrimerization of **4.187a-f** (Table 4.11).[65]



Scheme 4.31

Table 4.11 Co-Catalyzed Asymmetric Cross-Cyclotrimerization of 4.187

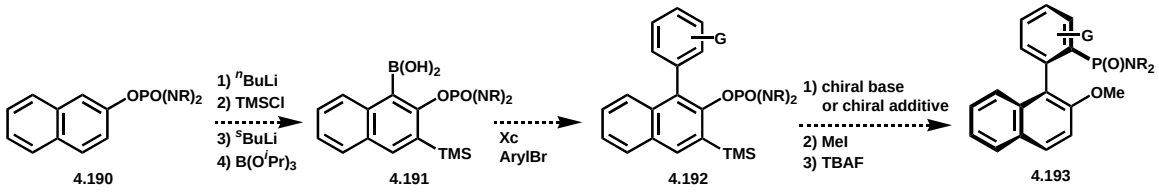


4.187a-f 4.188a-f 4.189a,b (for R = Ph and 4-MeOC$_6$H$_4$)

	R	4.188 (%)	%ee
a	Ph	49	79
b	4-MeOC$_6$H$_4$	51	72 (>99)[a]
c	3,5-(CF$_3$)C$_6$H$_4$	24	56
d	^{t}Bu	61	82 (>99)[a]
e	1-adamantyl	44	83 (>99)[a]
f	NMe$_2$	80	68

[a] After recrystallization

Since all of these compounds exist in the form of stable atropisomers at least up to 60 °C, their reduction to phosphines (**4.189a,b**) without erosion of enantiomeric excess appears to be an interesting approach to axially chiral *P*-ligands. This naturally suggests a close look at the possibility of developing an enantioselective phospha-DreM reaction through the use of chiral bases or chiral additives (Scheme 4.32).[66,67]



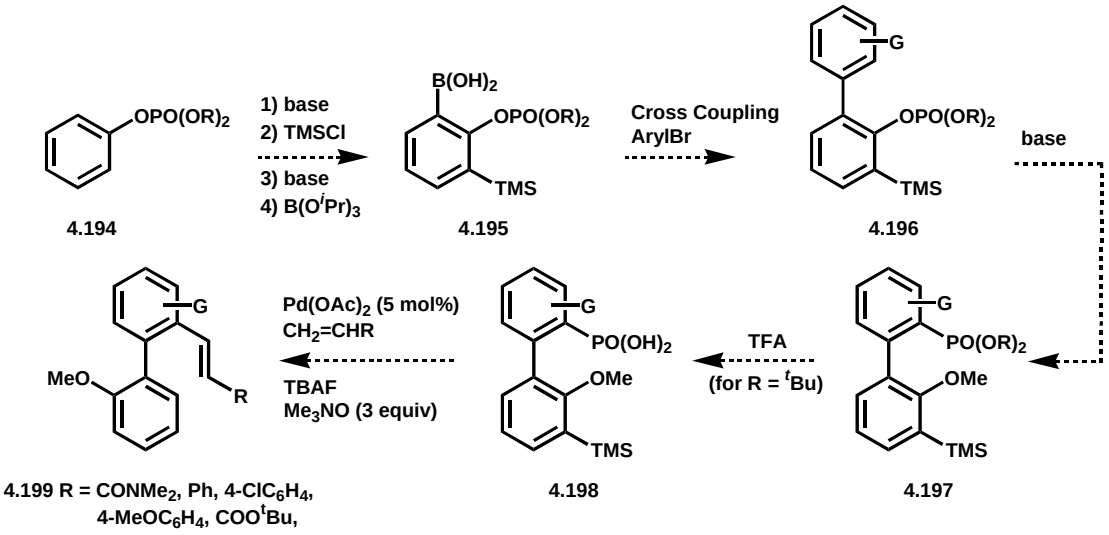
4.190 4.191 4.192 4.193

Scheme 4.32

The cross coupling of the OPO(NEt$_2$)$_2$ group is a relevant achievement because it allows its replacement with more desirable functionality while bypassing Knochel's manoeuvre for converting it into a reactive nonaflate group (Scheme 4.14). Scope definition of this reaction is necessary with particular attention to the lateral metalation/cross coupling link

for which the phosphorodiamidate group, compared to other *o*-DMGs, appears to be particularly suited.

As for the external trapping of *o*-lithiated aryl phosphates, there has been a clear lack of interest on this topic, which clashes with the numerous reports and applications of their phospha-Fries rearrangement. However, the behaviour of the $OPO(NEt_2)_2$ group in this regard may suggest that bulkier aryl phosphates may, at standard metalation temperatures, generate persistent and therefore more useful *o*-lithiated species. Virtually all 1,3-rearrrangements of aryl phosphates have been observed upon spontaneous warming of the reaction mixture to rt.[12a,c,14,68] As a result, it remains unknown whether di-*tert*-butyl or di-*iso*-propyl ary lphosphates, for example, by undergoing a slower rearrangement, are suitable substrates for D*o*M - subsequent external electrophile quench reactions. However, a study on the steric and electronic effects in the phospha-Fries rearrangement suggests that this process is indeed somewhat slower for bulkier phosphates.[69] In any case, anionic *o*-functionalization of diethyl aryl phosphates should be definitely tested with Knochel's Li/Mg mixed bases[30,31,70] and ate complexes[71] which are known to generate stable metalated species even at relatively high temperatures. In case of a positive outcome, the D*o*M of aryl phosphates may be easily linked to all post-D*o*M reactions (lateral migration of the phosphoryl group,[this work] Ni-catalyzed-cross coupling,[54,55] Pd-catalyzed reductive and hydrolytic cleavage[12c,68a,d,e]) for which encouraging precedents already exist. The DreM reaction of biaryl phosphates, if successful, may also be linked to the appealing oxidative Heck-type reaction which, through a C-P bond cleavage, removes the phosphoryl group and replaces it with versatile alkenyl substituents (**4.198** → **4.199**, Scheme 4.33).[72]



Scheme 4.33

4.5 Conclusions

Following Watanabe's development of the $OPO(NMe_2)_2$ DMG which requires metalation temperatures as low as −105 °C to prevent the facile 1,3 *O*→*C* rearrangement (**4.42a-h** → **4.43a-h**, Table 4.3), the hypothesis was formulated that a more hindered DMG may escape this fate at temperatures whereby the $OPO(NMe_2)_2$ group does not. Thus, metalation studies of the readily prepared tetraethyl aryl phosphorodiamidates **4.126a,b** (Scheme 4.18) were undertaken. The results show that: a) the bulkier bis(diethylamino)phosphoryl group resists the intramolecular *ortho*-migration under −78 °C metalation conditions but it undergoes quantitative migration at −30 °C (Scheme 4.18) presumably through the intermediacy of **4.200** (Fig. 4.4); b) at −78 °C, the *ortho*-lithiated derivatives of **4.126a,b** may be trapped with a wide range of electrophiles to furnish **4.127a-j** in 52-99 % yield (Scheme 4.18); c) as suggested by intermolecular competition experiments, the directing power of the $OPO(NEt_2)_2$ group is comparable to that of the

$OCONEt_2$ group (Scheme 4.19); d) both tolyl phosphate **4.141** and tolyl phosphorodiamidate **4.127i** undergo facile lateral metalation at −78 °C followed by a vinylogous *P*-Fries rearrangement which, for the latter, is remarkably slower, presumably due to a 10 kcal/mol difference in the energy barrier involved in the formation of the intermediate **4.201** (Fig. 4.4). This reaction furnishes valuable intermediates for the Horner-Wadsworth-Emmons and the Corey olefinations.

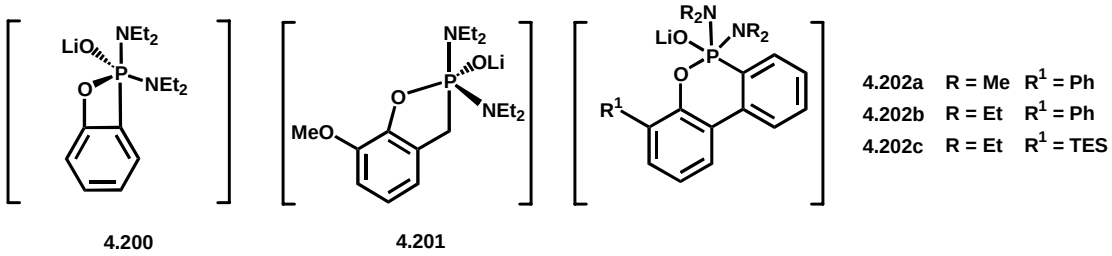


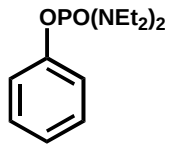
Figure 4.4 Pentacoordinated Intermediates Involved in the *Ortho*-, Vinylogous and Remote *P*-Fries Rearrangements

In a quest of further anionic reactions amenable to this new DMG, preliminary results obtained by Zumbansen and Lampert in the directed remote metalation of biaryl **4.168** (Table 4.7) and teraryl phosphorodiamidates **4.157b** (Table 4.6) show that the bis(dimethylamino) and bis(diethylamino)phosphoryl groups are capable of migration to the alternate ring, a process suggested to proceed via pentacoordinated phosphorus species **4.202a,c** (Fig. 4.4). Finally, drawing from several precedents in the cross coupling of aryl and vinyl phosphates, a preliminary ligand/catalyst screening was performed that, through Frendo-Cumbo's work, led to the establishment of a protocol for the Ni-catalyzed cross coupling of phosphorodiamidate **4.126a** with phenylboronic acid (Table 4.10).

Experimental Section

For General Methods see Section 2.7.

General Procedure A. Phenyl *N*,*N*,*N*',*N*'-tetraethylphosphorodiamidate (4.126a)

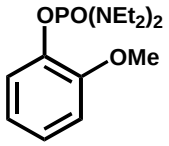


A 200 mL flask was charged with NaH (1.53 g, 38.26 mmol, 60% dispersion in mineral oil) and anhydrous THF (50 mL). To this cooled suspension (0 °C) was slowly added a solution of phenol (3 g, 31.88 mmol) in THF (10 mL) while allowing the escape of H_2 through a vent. The reaction mixture was stirred for 6 h at rt and $ClPO(NEt_2)_2$ (8.12 mL, 38.26 mmol) was then added. After stirring for additional 6 h at rt, the resulting reaction mixture was quenched with a satd aq soln of NH_4Cl (10 mL) and the organic layer was extracted with NaOH (30 mL, 1M aq soln), washed with brine and dried (Na_2SO_4). Solvent removal under reduced pressure and distillation of the oily residue gave 8.7 g (96% yield) of **4.126a** as a colorless oil, bp 125 °C/0.06 mm Hg; IR (film) ν_{max} cm^{-1} 2972, 1591, 1030, 777; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.31 (m, 4H), 7.09 (t, 1H, J = 7.8 Hz), 3.09-3.20 (m, 8H), 1.10 (t, 12H, J = 7.2); ^{13}CNMR (100 MHz, $CDCl_3$) δ 151.6 (d, J = 5.9 Hz), 129.4, 123.8, 120.2 (d, J = 5.1 Hz), 39.7 (d, J = 4.7 Hz), 14.1 (d, J = 2.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.4; LRMS *m/z* (rel intensity %) 284 (M^+, 24), 269 (100), 212 (66), 198 (44), 191 (37), 77 (25), 72 (36); HRMS calcd for $C_{14}H_{25}N_2O_2P$ 284.1654, found 284.1663.

General Procedure B for the Directed *ortho* Metalation of Aryl Phosphorodiamidates 4.126a,b

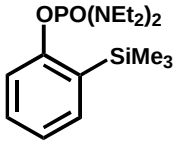
A solution of ^{s}BuLi (1.94 mmol, ~ 1.3 M) was added dropwise at −78 °C to a stirred solution of **4.126a or 4.126b (**1.76 mmol) in THF (5 mL). After stirring for 1 h at this temperature, the electrophile (1.94 or 2.11 mmol, neat or as a THF solution) was added, the reaction mixture was stirred for 20 min and allowed to warm to rt. Standard work up and purification yielded compounds **4.127a-j**.

2-Methoxyphenyl *N*,*N*,*N*',*N*'-tetraethylphosphorodiamidate (4.126b)



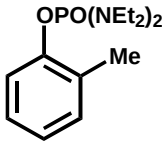
Prepared according to General Procedure A from guaiacol (**4.125b**, 2 g, 16.1 mmol), NaH (0.77 g, 19.33 mmol, 60% dispersion in oil) and $ClPO(NEt_2)_2$ (4.10 mL, 19.33 mmol). Standard work up and kugelrohr distillation of the crude residue (100 °C/0.06 mmHg) afforded 5.58 g (92% yield) of **4.126b** as a clear oil, bp 125-135 °C/0.06 mm Hg; IR (film) ν_{max} cm^{-1} 2971, 2878, 1594, 1504, 1031, 913, 792, 528; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, J = 7.9 Hz), 7.05 (t, 1H, J = 7.6 Hz), 6.91-6.86 (m, 2H), 3.83 (s, 3H), 3.12-3.21 (m, 8H), 1.10 (t, 12H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8 (d, J = 6.1 Hz), 140.9 (d, J =5.8 Hz), 124.3, 121.5 (d, J = 2.9 Hz), 120.7, 112.3, 55.8, 40.0 (d, J = 3.9 Hz), 39.7 (d, J = 4.8 Hz), 14.1 (d, J = 2.3 Hz), 13.5 (d, J = 3.5 Hz); MS *m/z* (rel intensity) 315 ($M\text{-}H^+$, 100), 242 (12), 191 (7); HRMS (calcd for $C_{15}H_{28}N_2O_3P$) 315.1838, found 315.1844.

2-(Trimethylsilyl)phenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127a)



Prepared according to general procedure B and using **4.126a** (0.5 g, 1.76 mmol) and TMSCl (0.27 mL, 2.11 mmol) as electrophile. Standard work up and chromatography (hexanes/EtOAc 4:1) yielded 0.58 g (84%) of **4.127a** as a colorless solid, mp 30-31 °C (hexanes/EtOAc); IR (film) ν_{max} cm^{-1} 2971, 1456, 1241, 842. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 1H, J = 8.4 Hz), 7.39 (d, 1H, J = 7.2 Hz), 7.30 (t, 1H, J = 8.0 Hz), 7.04 (t 1H, J = 7.2 Hz), 3.05-3.28 (m, 8H), 1.08 (t, 12 H, J = 6.8 Hz), 0.30 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (d, J = 6.0 Hz), 135.1, 129.6, 128.3 (d, J = 10.6 Hz), 122.7, 117.7 (d, J = 3.2 Hz), 39.2 (d, J = 4.6 Hz), 13.7 (d, J = 2.6 Hz), -0.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.1; MS *m/z* (rel intensity) 356 (3), 341 (100), 327 (19), 284 (20), 191 (83), 72 (53); HRMS (calcd for $C_{17}H_{33}N_2O_2PSi$) 356.2049, found 356.2050.

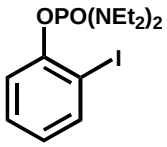
***o*-Tolyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127b)**



Prepared according to general procedure B and using **4.126a** (0.5 g, 1.76 mmol) and MeI (0.13 mL, 2.11 mmol) as electrophile. Standard work up and chromatography (hexanes/EtOAc 3:1) yielded 0.47 g (89%) of **4.127b** as a yellow oil, IR (film) ν_{max} cm^{-1} 2971, 1480, 1241, 784; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, 1H, J = 8.0 Hz), 7.14 (d, 1H, J = 7.2 Hz), 7.11 (t, 1H, J = 8.0 Hz), 6.96 (t, 1H, J = 7.2 Hz), 3.08-3.22 (m, 8H), 2.27 (s, 3H), 1.08 (t, 12H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (d, J = 6.0 Hz), 130.9, 128.2 (d, J = 7.6 Hz), 126.8, 123.3, 119.2 (d, J = 3.0 Hz), 39.7 (d, J = 4.7 Hz), 16.7, 14.0 (d, J = 2.3 Hz); ^{31}P NMR (162 MHz,

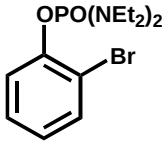
$CDCl_3$) δ 13.8; MS *m/z* (rel intensity) 298 (M^+, 16), 283 (47), 269 (4), 226 (21), 191 (57), 107 (20), 91 (32), 72 (100); HRMS (calcd for $C_{15}H_{27}N_2O_2P$) 298.1810, found 298.1819.

2-Iodophenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127c)



Prepared according to general procedure B and using **4.126a** (0.5 g, 1.76 mmol) and I_2 (0.53 g, 2.11 mmol) as electrophile. Standard work up and chromatography (hexanes/EtOAc 3:2 yielded 0.62 g (86%) of **4.127c** as a colorless solid, mp 43-44 °C (Hex/EtOAc), IR (KBr) ν_{max} cm^{-1} 2969, 1578, 1467, 1231, 1027, 904, 759, 542; ^1H NMR (400 MHz, $CDCl_3$) 7.66 (d, 1H, *J* = 8.0 Hz), 7.63 (d, 1H, *J* = 8.0), 7.18 (dt, 1H, *J* = 7.8 and 1.6 Hz), 6.71 (t, 1H, *J* = 7.6 Hz), 3.97-3.20 (m, 8H), 1.00 (t, 12H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7 (d, *J* = 4.4 Hz), 139.3, 129.3, 124.9, 119.7 (d, *J* = 2.8 Hz), 87.9 (d, *J* = 9.8 Hz), 39.6 (d, *J* = 4.8 Hz), 14.0 (d, *J* = 2.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.2; MS *m/z* (rel intensity) 410 (M^+, 16), 395 (100), 337 (79), 283 (48), 218(13), 191 (59); HRMS (calcd for $C_{14}H_{24}IN_2O_2P$) 410.0620, found 410.0634.

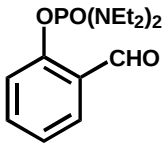
2-Bromophenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127d)



Prepared according to general procedure B and using **4.126a** (0.5 g, 1.76 mmol) and $(Br_2CH)_2$ (0.25 mL, 2.11 mmol) as electrophile. Standard work up and chromatography (hexanes/EtOAc 13:7) yielded 0.43 g (67%) of **4.127d** as a colourless oil, IR (film) ν_{max} cm^{-1} 2972, 1470, 1375, 1240, 1031, 792, 759, 534; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 1 H, *J* = 8.0 Hz), 7.54 (d, 1 H, *J* = 8.0 Hz), 7.26 (t, 1H, *J* = 7.6 Hz), 6.96 (t, 1H, *J* = 7.6 Hz), 3.10-3.31 (m, 8H), 1.10 (t, 12H, *J*

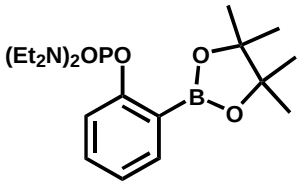
= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0 (d, J = 4.5 Hz), 133.3, 128.4, 124.5, 120.9 (d, J = 2.9 Hz), 113.8 (d, J = 9.0 Hz), 39.6 (d, J = 4.9 Hz), 14.0 (d, J = 2.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.2; MS *m/z* (rel intensity) 364 (M+2, 8), 362 (M^+, 8), 349 (53), 347 (54), 292 (45), 290 (45), 278 (37), 276 (37), 191 (100); HRMS (calcd for $C_{14}H_{24}N_2O_2PBr$-H^+) 363.0837, found 363.0836.

2-Formylphenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127e)



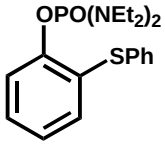
Prepared according to general procedure B and using **4.126a** (0.5 g, 1.76 mmol) and anhydrous DMF (0.15 mL, 1.94 mmol) as electrophile. Standard work up and passage through a short silica plug (hexanes/EtOAc 3:2) yielded 0.54 g (98%) of **4.127e** as a clear oil, IR (film) ν_{max} cm^{-1} 2972, 1693, 1600, 1478, 1375, 1243, 1212, 1194, 1026, 905; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 7.86 (d, 1H, J = 7.5 Hz), 7.72 (d, 1H, J = 8.4 Hz), 7.56 (dt, 1H, J = 7.8 and 1.8 Hz), 7.20 (t, 1H, J = 7.5 Hz), 3.0-3.25 (m, 8H), 1.10 (t, 12H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 154.3, 135.7, 128.5, 126.7, 123.8, 120.7, 39.6, 14.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.6; MS *m/z* (rel intensity) 283 (5), 269 (30), 240 (77), 212 (32), 191 (38), 176 (36), 72 (100); HRMS (calcd for $C_{15}H_{25}N_2O_3P$) 312.1603, found 312.1617.

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl *N*,*N*,*N*',*N*'-tetraethylphosphorodiamidate (4.127f)



Prepared according to general procedure B and using **4.126a** (0.5 g, 1.76 mmol) and $B(O^iPr)_3$ (0.49 mL, 2.11 mmol) as electrophile. The reaction mixture was then treated with pinacol (0.31 g, 2.64 mmol) and was stirred for 10 h. Standard work up and chromatography (hexanes/EtOAc 1:1) yielded 0.377 g (52%) of **4.127f** as a colorless solid, mp 62-63 (hexanes); IR (film) ν_{max} cm^{-1} 2975, 1590, 1452, 923; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 1H, J = 7.6 Hz), 7.70 (d, 1H, J = 8.4 Hz), 7.36 (t, 1H, J = 8.0 and 1.6 Hz), 7.06 (t, 1H, J = 7.2 Hz), 3.09-3.28 (m, 8H), 1.32 (s, 12H), 1.03 (t, 12H, J= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 136.8, 132.4, 123.1, 119.8 (d, J = 3.1 Hz), 83.4, 39.3 (d, J = 5 Hz), 24.9, 14.0 (d, J = 2.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.6; MS *m/z* (rel intensity) 410 (M^+, 1), 395 (18), 381 (26), 352 (100), 323 (23), 281 (36), 246 (91), 72 (38); HRMS (calcd for $C_{20}H_{36}BN_2O_4P$-H^+) 411.2584, found 411.2599.

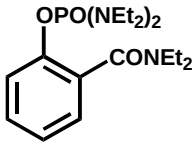
2-(Phenylthio)phenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127g)



Prepared according to general procedure B and using **4.126a** (0.5 g, 1.76 mmol) and (after a metalation time of 2 h) PhSSPh (1.15 g, 5.28 mmol in 5 mL of anhydrous THF) as electrophile. Standard work up and chromatography (hexanes/EtOAc 3:1) yielded 0.53 g (77%) of **4.127g** as a clear oil, IR (film) ν_{max} cm^{-1} 2971, 1471, 1241, 1210, 1200, 1172, 1025, 908, 753; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 8.4 Hz), 7.20-7.35 (m, 6H), 7.08-7.18 (m, 1H), 7.00 (t, 1H, J = 7.2 Hz), 3.00-3.27 (m, 8H), 1.50 (t, 12H, J = 6.9 Hz); ^{13}CNMR (100 MHz,

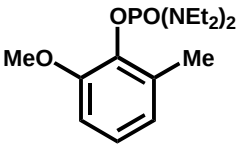
$CDCl_3$) δ 150.3, 134.6, 132.1, 130.8, 129.2, 128.4, 127.0, 124.0, 120.2, 119.9, 39.5, 13.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.8; LRMS *m/z* (rel intensity %) 392 (M^+, 32), 320 (100), 283 (23), 248 (26), 191 (32), 72 (32); HRMS calcd for $C_{20}H_{29}N_2O_2PS$ 392.1687, found 392.1687.

2-(Diethylcarbamoyl)phenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127h)



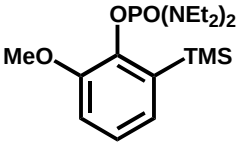
Prepared according to general procedure B and using **4.126a** (0.5 g, 1.76 mmol) and $ClCONEt_2$ (0.267 mL, 2.11 mmol) as electrophile. Standard work up and chromatographic separation (hexanes/EtOAc 1:1) yielded 0.42 g (61%) of **4.127f** as a clear oil, IR (film) ν_{max} cm^{-1} 2973, 2935, 2875, 1638, 1381, 1295, 1241, 1033, 915; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H, *J* = 8.4 Hz), 7.30 (dt, 1H, *J* = 7.8 and 1.6 Hz), 7.19 (d, 1H, *J* = 7.2 Hz), 7.1 (t, 1H, *J* = 7.2 Hz), 3.52-3.66 (m, 1H), 3.40-3.52 (m, 1H), 2.96-3.30 (m, 10H), 1.25 (t, 3H, *J* = 7.2 Hz), 1.13 (t, 6H, *J* = 7.2 Hz), 1.04 (t, 3H, *J* = 6.8 Hz), 0.96 (t, 6H, *J* = 6.8 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ 168.0, 147.7 (d, *J* = 5.6 Hz), 129.7, 128.6 (d, *J* = 8.4 Hz), 127.2, 123.5, 119.8 (d, *J* = 3.1 Hz), 43.2, 39.5, 39.3, 14.2, 14.1, 13.6, 13.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.6; LRMS *m/z* (rel intensity %) 383 (M^+, 1), 311 (100), 283 (27), 240 (85), 205 (16), 192 (13), 72 (43); HRMS calcd for $C_{19}H_{34}N_3O_3P$ 383.2338, found 383.2345.

2-Methoxy-6-methylphenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127i)



Prepared according to general procedure B and using **4.126b** (0.55 g, 1.76 mmol) and MeI (0.13 mL, 2.11 mmol) as electrophile. Standard work up and chromatography (hexanes/EtOAc 2:1) yielded 0.51 g (88%) of **4.127i** as a yellow oil, IR (neat) ν_{max} cm^{-1} 2981, 2363, 1474, 1210, 1023, 894, 766, 534. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (t, 1H, J = 7.9 Hz), 6.78 (d, 1H J = 8.0 Hz), 6.74 (d, 1H, J = 7.9 Hz), 3.82 (s, 3H), 3.08-3.29 (m, 8H), 2.41 (s, 3H), 1.11 (t, 12H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 139.4, 132.1 (d, J = 3.4 Hz), 124.3 (d, J = 1.8 Hz), 123.2, 109.8, 55.6, 39.8, 17.7, 14.2 (d, J = 2.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.9; MS *m/z* (rel intensity): 329 ($M\text{-}H^+$, 100), 313 (13), 256 (47), 191 (15); HRMS (calcd for $C_{16}H_{30}N_2O_3P$) 329.1994, found 329.1984.

2-Methoxy-6-(trimethylsilyl)phenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (4.127j)



Prepared according to general procedure B and using **4.126b** (0.55 g, 1.76 mmol) and TMSCl (0.27 mL, 2.11 mmol) as the electrophile. Standard work up and chromatography (hexanes/EtOAc 3:2) yielded 0.58 g (86%) of **4.127j** as colourless crystals, mp 76-77 °C (hexanes/EtOAc); IR (neat) ν_{max} cm^{-1} 2978, 2950, 2896, 2867, 1571, 1429, 1268, 1237, 1172, 1028, 907; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dt, 1H, J = 8.0 and 0.8 Hz), 6.99 (ddd, 1H, J = 7.3 and 2.0 and 0.8 Hz), 6.93 (dd, 1H, J = 8.0 and 1.6 Hz), 3.82 (s, 3H), 3.04-3.2 (m, 8H), 1.05 (t, 12H, 7.2 Hz), 0.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, (d. J = 3.0 Hz), 145.4 (d, J = 8.0 Hz), 133.1 (d, J = 5.0 Hz), 127.0, 124.3, 114.1, 55.7, 40.2 (d, J = 5.0 Hz),

14.3, (d, J = 2.0 Hz), 0.00; MS *m/z* (rel intensity) 386 (8), 372 (69), 371 (100), 314 (34), 191 (87); HRMS (calcd for $C_{18}H_{35}N_2O_3PSi$) 386.2155, found 386.2151.

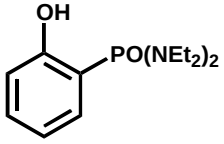
Intermolecular Competition Experiment for 4.126a and 4.129

A 25 mL flame-dried flask was charged with a solution of **4.126a** (0.467 mL, 1.76 mmol) and **4.129** (0.323 mL, 1.76 mmol) in THF (10 mL). To this cooled (–78 °C) and vigorously stirred solution was dropwise added ^{s}BuLi (1.41 mL, 1.85 mmol, 1.315 M). After stirring for 1 h, CD_3OD (0.11 mL, 2.64 mmol) was added and the reaction mixture was allowed to warm to 0 °C. Standard work up and chromatography (hexanes/EtOAc 17:3) afforded 0.31 g (90%) of **4.131/4.129** and 25 mg (5%) of **4.132**. Further elution of the column with EtOAc yielded 0.43 g (86%) of **4.130/4.126a**. The ^{1}H NMR spectrum of the mixture **4.130/4.126a** displayed the following signals: (400 MHz, $CDCl_3$) δ 7.22-7.31 (m, 3.5H, H_2-H_3), 7.09 (t, 1H, J = 7.8 Hz, H_4), 3.09-3.20 (m, 8H), 1.10 (t, 12H, J = 7.2) and its deuterium content was calculated as follows:

$$\frac{\textbf{4.130}}{\textbf{4.126a}} = \frac{\begin{array}{l}\text{4.0 (theoretical area for } H_2\text{-}H_3 \text{ peak at 7.22-7.31 } \delta \text{ -} \\ \text{3.5 (area for } H_2\text{-}H_3 \text{ peak at 7.22-7.31 } \delta \text{ (m, } \textbf{4.130}\text{+}\textbf{4.126a}\text{)}\end{array}}{\text{1.0 (area for } H_4 \text{ peak at 7.09 (t, } J = 7.8 \text{ Hz) for } \textbf{4.130}\text{+}\textbf{4.126a}\text{)}} = \textbf{0.5}$$

An analogous method was used to calculate the deuterium content of the mixture of **4.131/4.129**.

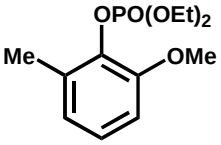
***N*,*N*,*N*',*N*'-Tetraethyl-2-hydroxyphenylphosphonic diamide (4.128)**



A solution of ^{s}BuLi (3.70 mmol, ~ 1.3 M in cyclohexane) or, alternatively, a solution of LDA (3.70 mmol, ~ 0.7 M in THF) was added dropwise to a stirred solution of **4.126a** (0.5 g, 1.76 mmol) in

THF (5 mL) at –78 °C. After stirring for 1h at this temperature, the reaction mixture was allowed to warm to rt. Standard work up yielded, without separation, 0.49 g (98%) of **4.128** as clar oil, IR (neat) ν_{max} cm^{-1} 2974, 2932, 2873, 1576, 1453, 1301, 1251, 1206, 1128, 1021, 950, 762, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0-12.0 (bs, 1H), 7.33 (dt, 1H, J = 8.0 and 1.2 Hz), 7.23 (ddd, 1H, J = 14.8, 9.6 and 2.0 Hz), 6.91 (dd, 1H, J = 8.0 and 5.2 Hz), 6.80 (ddt, 1H, J = 8.0, 3.2 and 1.2 Hz), 3.05-3.17 (m, 8H), 0.96-1.13 (t, 12H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 133.5, 130.9, 118.45 (d, J = 9.8 Hz), 117.8, 113.1 (d, J = 150 Hz), 38.4, 13.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.5; MS *m/z* (rel intensity): 284 (M^+, 53), 267 (10), 212 (91), 196 (29), 184 (29), 72 (100); HRMS (calcd for $C_{14}H_{25}N_2O_2P$) 284.1654, found 284.1657.

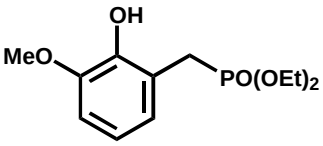
Diethyl 2-methoxy-6-methylphenyl phosphate (4.141)



Prepared according to general procedure A from 2-methoxy-6-methylphenol[73] (**4.140**, 5 g, 36.23 mmol), NaH (1.74 g, 43.5 mmol, 60% dispersion in oil) and $ClPO(OEt)_2$ (6.28 mL, 43.5 mmol). The crude mixture was washed with NaOH (60 mL, 1M), with brine and dried (Na_2SO_4). Recrystallization of the crude residue afforded 7.54 g (76% yield) of **4.141** as colourless crystals, mp 51-52 °C (hexanes); IR (film) ν_{max} cm^{-1} 2985, 2941, 2843, 1606, 1584, 1495, 1437, 1296, 1280, 1204, 1184, 1084, 1065, 1033, 929, 783; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dt, 1H, J = 8.0 and 1.2 Hz), 6.77 (d, 1H, J = 8.1 Hz), 6.65 (d, 1H, J = 7.6 Hz),4.21-4.29 (m, 4H), 3.84 (s, 3H), 2.40 (s, 3H), 1.36 (dt, 3H, J = 7.2 and 0.4 Hz), 1.358 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1 Hz), 138.9 (d, J = 7.8 Hz), 131.2 (d, J = 3.8 Hz), 125.1, 122.9, 110.1, 64.2 (d, J = 6.0 Hz), 55.8 (d, J = 6.0 Hz), 16.5

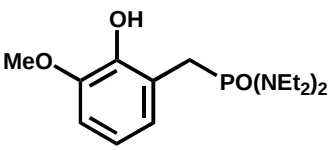
(d, J = 5.2 Hz), 16.0 (d, J = 5.7 Hz); MS *m/z* (rel intensity) 274 (100), 246 (27), 228 (31), 217 (46), 200 (69), 199 (51), 187 (31), 185 (28), 155 (55), 133 (54), 127 (45); HRMS (calcd for $C_{12}H_{19}O_5P$) 274.0970, found 274.0970.

Diethyl 2-hydroxy-3-methoxybenzylphosphonate (4.142)



^{s}BuLi (1.64 mL, 2.31 mmol, 1.40 M in cyclohexane) was added to a solution of **4.141** (0.3 g, 1.10 mmol) in THF (5 mL) at –78 °C. After stirring at –78 °C for 1h, the reaction mixture was allowed to warm to 0 °C and was quenched with a satd aq soln of NH_4Cl. Standard work up gave 0.297 (99%) of **4.142** as clear oil, IR (film) ν_{max} cm^{-1} 3266, 2985, 2946, 2915, 1591, 1483, 1275, 1234, 1054, 1027, 967; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75-6.87 (m, 3H), 6.71 (s, 1H), 3.98-4.11 (m, 4H), 3.88 (s, 3H), 3.23 (s, 2H, J = 28.4 Hz), 1.25 (t, 3H, J = 9.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5 (d, J = 3.0 Hz), 144.1 (d, J = 6.6 Hz), 123.1 (d, J = 5.6 Hz), 119.6 (d, J = 2.7 Hz), 118.0 (d, J = 8.9 Hz), 109.7 (d, J = 3.0 Hz), 62.1 (d, J = 6.6 Hz), 55.8, 27.8, 26.7, 16.1 (d, J = 5.9 Hz); MS *m/z* (rel intensity) 274 (56), 228 (92), 201 (72), 200 (100), 185 (90), 135 (44); HRMS (calcd for $C_{12}H_{19}O_5P$) 274.0970, found 294.0974.

***N,N,N,'N'*-Tetraethyl-*P*-(2-hydroxy-3-methoxybenzyl)phosphonic diamide (4.143)**



A flame-dried 25 mL flask was charged with DIPA (0.92 mL, 6.60 mmol), TMEDA (0.82 mL, 5.49 mmol) and anhydrous hexanes (6 mL), To this stirred mixture at 10 °C was added ^{n}BuLi (2.20 mL, 5.49 mmol, 2.5 M) and the reaction mixture was stirred at for 15min. A

solution of **4.127i** (0.6 g, 1.83 mmol) in anhydrous ether (1 mL) was slowly added to the stirred solution of LDA at 0 °C and the reaction mixture was stirred at rt for 8 h. Standard work up yielded a solid which was recrystallized to give 0.52 g (87%) of **4.143** as colourless flakes, mp 122-124 °C (hexanes/EtOAc), ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 6.71-7.82 (m, 2H), 6.61 (d, 1H, J = 6.9 Hz), 3.86 (s, 3H), 3.22 (d, 2H, J = 16.2 Hz), 2.92-3.11 (m, 8H), 1.02 (t, 12H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2 (d, J = 3.6 Hz), 146.2 (d, J = 5.4 Hz), 123.5 (d, J = 8.5 Hz), 121.1 (d, J = 9.5 Hz), 119.6 (d, J = 1.9 Hz), 111.0 (d, J = 3.1 Hz), 56.0, 38.7 (d, J = 4.8 Hz), 31.7 (d, J = 135.7 Hz), 14.0 (d, J = 3.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.73; LRMS (EI, 70 eV) *m/z* (rel intensity) 328 (20), 313 (4), 297 (5), 281 (7), 256 (100), 164 (41); HRMS (calcd for $C_{16}H_{29}N_2O_3P$) 328.1916, found 328.1911.

4.7 References

[1] Christensen, H. *Synth. Commun.* **1975**, *5*, 65-78.

[2] Stern, R.; English, J.Jr.; Cassidy, H.G.; *J. Am. Chem. Soc.* **1957**, *79*, 5797-5800. Harris, T.D.; Oruganti, S.R.; Davis, L.M.; Keehu, P.M.; Green, B.S. *Tetrahedron* **1987**, *43*, 1519-1540. Azzouz, R.; Bischoff, L.; Fruit, C.; Marsais, F. *Synlett* **2006**, 1908-1912.

[3] Sengupta, S.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 4267-4270.

[4] Nerdinger, S.; Kendall, C; Cai, X.; Marchart, R.; Riebel, P.; Johnson, M.R.; Yin, C.-F.; Henaff, N.; Eltis, L.D.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 5960-5967. Lira, R.; Xiang, A.X.; Doundoulakis, T.; Biller, W.; Agrios, K.A.; Simonsen, K.B.; Webber, S.E.; Sisson, W.; Aust, R.M.; Shah, A.M.; Showalter, R.E.; Banh, V.N.; Steffy, K.R.; Appleman, J.R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6797-6800. Graves, C.R.; Zhou, H.; Stern, C.L.; Nguyen, S.T. *J. Org. Chem.* **2007**, *72*, 9121-9133. Zhou, J.; Lobera, M.; Neubert-Langille, B.J.; Snider, B.B. *Tetrahedron* **2007**, *63*, 10018-10024.

[5] Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* **1938**, *61*, 109-112. Wittig, G.; Pockels, U.; Droge, H *Chem. Ber.* **1938**, *71B*, 1903-1912.

[6] Sengupta, S.; Leite, M.; Raslan, D.S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066-4068.

[7] Macklin, T.K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519-2522.

[8] Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183- 1186.

[9] Kaush, M.; Hoppe, D. *Can. J. Chem.* **2001**, *79*, 1736-1746.

[10] Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519-2522. Macklin, T.K. Ph.D. Thesis, Queen's University, Kingston, Canada, 2007.

[11] a) For $OCONEt_2$: Sibi, M. P.; Snieckus, V. *J. Org. Chem*. **1983**, *48*, 1935-1937. b) For $OCONMeC(Me)_2Ph$: Ref. 8. c) For $OCON(TMS)^iPr$: Ref 9.

[12] For $OPO(OEt)_2$: a) Melvin, L.S.; *Tetrahedron Lett.* **1981**, *22*, 3375-3376. b) Cambie, R.C.; Palmer, B.D. *Aust. J. Chem.* **1982**, *35*, 827-837. c) Dhawan, D.; Redmore, D. *J. Org. Chem.* **1984**, *49*, 4018-4021 and **1986**, *51*, 179-183 and **1991**, *56*, 833-835. d) For $OPO(NMe_2)_2$: Watanabe, M.; Date, M.; Kawanishi, K.; Hori, T.; Furukawa, S. *Chem. Pharm. Bull.* **1990**, *38*, 2637-2643. Watanabe, M.; Date, M.; Kawanishi, K.; Tsukazaki, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 2564-2566.

[13] Review: Taylor, C.M.; Watson, A.J. *Curr. Org. Chem.* **2004**, *8*, 623-636.

[14] Dhawan, D.; Redmore, D. *Synth. Commun.* **1987**, *17*, 465-468.

[15] Further support to this conclusion came from a crossover experiment: Heinicke, J. Böhle, I.; Tzschach, A. *J. Organomet. Chem.* **1986**, *317*, 11-21.

[16] Jardine, A.M.; Wather, S.M. Modro, T. *J. Org. Chem.* **1988**, *53*, 3983-3985.

[17] Näsman, J.H.; Kopola, N.; Pensar, G. *Tetrahedron Lett.* **1986**, *27*, 1391-1394.

[18] Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897-7900.

[19] Barbosa, L.C.A.; Rocha, M.E.; Teixeira, R.R.; Maltha, C.R.A.; Forlani, G. *J. Agric. Food. Chem.* **2007**, *55*, 8562-8569.

[20] Winkle, M.R.; Ronald, R.C. *J. Org. Chem.* **1982***, 47*, 2101-2108.

[21] Snieckus, V. *Heterocycles* **1980**, *14*, 1649-1676 Beak, P.; Snieckus, V. *Acc. Chem, Res.* **1982**, *15*, 306-312.

[22] a) Date, M.; Kawanishi, K.; Hori, T.; Watanabe, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 2884-2886. b) Watanabe, M.; Date, M.; Kawanishi, K.; Hori, T.; Furukawa, S. *Chem. Pharm. Bull.* **1991**, *39*, 41-48.

[23] No mechanistic investigation was carried out. For comparison, **4.44d-Me** underwent lateral metalation and quench with methylbenzoate to give **4.63** (R = OMe, Ar = Ph) in 67% yield (Scheme 3.9).

[24] a) Legrand, O.; Brunel, J.M.; Buono, G. *Eur. J. Org. Chem.* **1999**, 1099-1105 and b) *Tetrahedron Lett.* **1998**, *39*, 9419-9422 and c) *Tetrahedron* **2000**, *56*, 595-603. d) Legrand, O.; Brunel, J.M.; Constantieux, T.; Buono, G. *Chem. Eur. J* **1998***, 4*, 1061-1067.

[25] Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127-153.

[26] a)He, K.; Zhou, Z.; Wang, L.; Li, K.; Zhao, G.; Zhou, Q.; Tang, C. *Tetrahedron* **2004**, *60*, 10505-10513 and b) *Synlett* **2004**, *9*, 1521-1524. c) Yang, Z.; Zhou, Z.; He, K.; Wang, L.; Zhao, G.; Zhou, Q.; Tang, C. *Tetrahedron: Asymmetry* **2003**, *14*, 3937-3941.

[27] Hatano, M.; Miyamoto, T.; Ishihara, K. *J. Org. Chem.* **2006**, *71*, 6474-6484 and *Synlett* **2006**, *11*, 1762-1764.

[28] Westheimer, F.H. *Acc. Chem. Res.* **1968**, *1*, 70-78.

[29] Berry, R.S. *J. Chem. Phys.* **1960**, *32*, 933-938.

[30] Clososki, G.C.; Rohbogner, C.J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684.

[31] Rohbogner, C.J.; Clososki, G.C.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1503-1507.

[32] Ireland, R.; Muchmore, D.C.; Hengartner, U. *J. Am Chem. Soc.* **1972**, *94*, 5098-5100.

[33] (a) *Anionic ortho-Fries*: see Ref. 11a. (b) *Vinylogous anionic ortho-Fries*: Kalinin, A. V.; Miah, M. A. J.; Chattopadhyay, S.; Tsukazaki, M.; Wicki, M.; Nguen, T.; Coelho, A. L.; Kerr, M.; Snieckus, V. *Synlett* **1997**, *7*, 839-841. (c) *1,5-O→O CONEt$_2$ translocation*: Chauder, B. A.; Kalinin, A. V.; Taylor, N. J.; Snieckus, V. *Angew. Chem. Int. Ed*. **1999**, *38*, 1435-1438. (d) *Remote anionic Fries*: Wang. W.; Snieckus, V. *J. Org. Chem*. **1992**, *57*, 424-426. (e) *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.

[34] Puterbaugh, W.H.; Hauser, C.R. *J. Org. Chem.* **1964**, *29*, 853-856.

[35] Comins, D. L. *Synlett* **1992**, 615-625 and references therein; Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1989**, *54*, 3730-3732.

[36] Caron, S.; Hawkins, J.M. *J. Org. Chem.* **1998**, *63*, 2054-2055. Krizan, T.D.; Martin, J.C. *J. Am. Chem. Soc.* **1983,** *105*, 6155-6157; Section 1.7 of this thesis.

[37] Beak, P.; Brown, R.A. *J. Org. Chem.* **1977**, *42*, 1823-1824.

[38] Comins, D.L.; Brown J.D. *I. Org. Chem.* **1986**, *51*, 3566-3572.

[39] Cuevas, J.-C.; Patil, P.; Snieckus, V. unpublished results.

[40] Cuevas, J.-C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5841-5844.

[41] Friedman, O.M.; Seligman, A.M. *J. Am. Chem. Soc.* **1950**, *72*, 624-625

[42] $ClPO(NMe_2)_2$ is available from most fine chemical suppliers. $ClPO(NEt_2)_2$ can be purchased from Alfa Aesar and Acros Organics.

[43] Kristina Zumbansen, visiting student, Universität Münster, Germany.

[44] Corey, E.J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* **1966**, *88*, 5652-5653 and **1968**, *90*, 6816-6821. Corey, E.J.; Cane, D.E. *J. Org. Chem.* **1969**, *34*, 3053-3057. Petrova, J.; Kirilov, M.; Momchilova, S.; Kossev, K. *Phosphorus Sulfur Silicon Relat. Elem.* **1998**, *40*, 69-74. Momchilova, S.; Petrova, J.; Kirilov, M. *Phosphorus Sulfur Silicon Relat. Elem.* **1988**, *35*, 319-327.

[45] I am particularly grateful to Dr. Nick Mosey for performing these calculations.

[46] Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206-2225.

[47] Zumbansen, K. Final Report, Queen's University, 2005.

[48] For example: Toshiyuki, K.; Yoshinobu, S.; Hironori, Y.; Kiyotaka, S. Patent no. WO 2006126393 (2006). Feng, L.; Anbin, T.; Zigui, X.; Shiwen, L. Patent no. CN 100999145 (2007).

[49] a) Qureshi, A.; Hay, A.S. *J. Chem. Res. (S)*, **1998**, 355. b) Keglevich, G.; Szelke, H.; Kerényi, A.; Kudar, V.; Hanusz, M.; Simon, K.; Imre, T.; Ludányi, K. *Tetrahedron: Asym.* **2005**, *16*, 4015-4021.

[50] Ryu, S.; Jackson, J.A.; Thompson, C.M. *J. Org. Chem.* **1991**, *56*, 4999-5002.

[51] Blackburn, T., Snieckus, V. Unpublished results.

[52] Puumala, K.A., M.Sc. Thesis, University of Waterloo, Canada, 1997.

[53] Milburn, R. R.; Snieckus, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 888-891.

[54] a) Hayashi, T.; Katsuro, Y.; Okamoto, Y.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 4449-4452. b) Huang, W.G.; Jiang, Y.Y.; Li. Q.; Li, J.; Li, J.Y.; Lu, W.; Cai, J.C. *Tetrahedron* **2005**, *61*, 1863-1870.

[55] Schwier, T.; Sromek, A.W.; Yap, D.M.L.; Chemyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868-9878.

[56] Armstrong, R.J.; Harris, F.L.; Weiler, L. *Can J. Chem.* **1982**, *60*, 673-675. Sahlberg, C.; Quader, A.; Claesson, A. *Tetrahedron Lett.* **1983**, *24*, 5137-5138. Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001-1003.

[57] a) Nicolaou, K.C.; Shi, G.-Q.; Gunzner, J.L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467-5468. b) Claveau, E.; Gillaizeau, I.; Blu, J.; Bruel, A.; Coudert, G. *J. Org. Chem.* **2007**, *72*, 4832-4836.

[58] a) Original study: Nan, Y.; Yang, Z. *Tetrahedron Lett.* **1999**, *40*, 3321-3324. Recent examples: b) Fuwa, H.; Sasaki, M. *Org. Lett.* **2007**, *9*, 3347-3350. c) Hansen, A.L.; Ebran, J.-P.; Gøgsig, T.M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464-6472.

[59] Yang, Z.; Wu, J. *J. Org. Chem.* **2001**, *66*, 7875-7878.

[60] Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983-14992.

[61] Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2001**, *57*, 6969-6975.

[62] Blackburn, T.; Frendo-Cumbo, J.; Snieckus, V. unpublished results. See Frendo-Cumbo, J. Chemistry 4XX Report, 2008.

[63] Hansen, A.L.; Ebran, J.-P.; Gogsig, T.M.; Skrydstrup, T. *Chem. Commun.* **2006**, 4137-4139.

[64] Martin, R.; Buchwald, S.L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

[65] Heller, B.; Gutnov, A.; Fisher, C.; Crexler, H.-J.; Spannenberg, A.; Redkin, D.; Sundermann, C.; Sundermann, B. *Chem. Eur. J.* **2007**, *13*, 1117-1128.

[66] ^{n}BuLi is known to effect C_3-metalation of 2-Naphthyl-*N*,*N*,*N*',*N*'-tetramethylphosphorodiamidate, see: Näsman, J.H.; Kopola, N. *Synth. Commun.* **1992**, *22*, 2491-2498.

[67] Price, D.; Simpkins, N. S. *Tetrahedron Lett.* **1995**, *36*, 6135-6136. Quattorpani, A.; Bernardinelli, G.; Künding, E. P. *Helv. Chim. Acta* **1999**, *82*, 90-104. Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685-686. Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899-2902.

[68] a) Dhawan, B.; Redmore, D. *Synth. Commun.* **1985**, *15*, 411-416; b) *J. Chem. Res. Synop.* **1988**, 222-222 and c) **1990**, 184; d) *Phosphorus, Sulfur, Silicon, Relat. Elem.* **1989**, *42*, 177-182 and e) **1991**, *61*, 183-187.

[69] Casteel, D.A.; Peri, S.P. *Synthesis* **1991**, 691-693.

[70] Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958-2961. Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673-5676.

[71] For a review see: Mulvey, R.E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed*. **2007**, *46*, 3802-3824.

[72] Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 1484-1485.

[73] Stevens, R.V.; Angle, S.R.; Kloc, K.; Mak, K.F.; Liu, Y.X.; Trueblood, K.N. *J. Org. Chem.* **1986**, *51*, 4347-4353.

CHAPTER 5

5.1. Summary and Conclusions

The Directed *ortho* Metalation can be safely described as the reaction with the highest impact on the development of aromatic chemistry since the electrophilic aromatic substitution. Perhaps not surprisingly, the reasons of such success may be found in what its major competitor, the EAS, lacks most, high regioselectivity. Section 1.1 offers an overview of this reaction with particular emphasis on its mechanism, its connections to other reactions, and its applications in different fields of chemistry. The most common application of D*o*M is arguably the synthesis of (hetero)biaryls, whose preparation would otherwise require very costly and convoluted approaches. For azabiaryls, many of these are described in Section 2.1 followed by a review of the D*o*M of DMG-bearing pyridines with particular emphasis on the $CONR_2$ DMG. The original research described in Section 2.4 defines effective experimental conditions for the *ortho*-borylation of diethyl pyridine carboxamides **2.263a-c** (Table 2.6) that prevent the otherwise unavoidable selfcondensation to benzophenone-type products (**2.264-2.266**, Scheme 2.53). This undesired reaction, which has no parallel in the metalation of diethylbenzamides, can be simplistically rationalized with the negative inductive effect of the pyridine ring which renders the carbonyl group more electrophilic. The above selfcondensation has been circumvented with the use of the bulkier diisopropyl pyridine carboxamides (Scheme 2.47). However, the price of this choice may be paid at a later stage with lower yields of conversion if, as frequently is the case, the bulky amide group of an advanced intermediate is expected to undergo modification through hydrolysis, reduction, cyclization and other reactions that suffer the effect of hindrance. Thus, our method,

based on the *in situ* electrophilic quench technique established by Martin[1] and Hawkins,[2] shows that the $CONEt_2$ group is still a valuable DMG for the silylation and borylation of pyridines. These metalation conditions were extended to the borylation of pyridines bearing F, Cl, and the $OCONEt_2$ group as DMG (**2.351-2.353**, Table 2.9) and all the boropinacolates obtained were subjected, without isolation, to Pd-catalyzed cross coupling with a series of (hetero)aryl bromides bearing EDG- and EWG-groups. Thus, while avoiding the tedious and low-yielded isolation of the boronic acid intermediates, this one-pot DoM-boronation-Suzuki-Miyaura cross coupling of pyridines offers direct access to synthetically valuable azabiaryls **2.354a-s** in generally higher yields when using deactivated aryl bromide coupling partners and lower yields when coupling dimethoxybromobenzene and *p*-nitronromobenze (Table 2.9). The D*o*M-DreM nexus was demonstrated using selected aryl pyridine carboxamides (**2.354b,e,h,k**) which, upon intramolecular anionic condensation, yield substituted and isomerically diverse azafluorenones (**2.380a-d**, Table 2.11). Once again, regioselectivity was a remarkable feature of this reaction as illustrated by the DreM of 3'-substituted azabiaryls **2.354h** and **2.354k** which, under the directing effects of the OMe and the Cl DMGs respectively, in synergistic combination with a CIPE on the $CONEt_2$ group, exclusively yielded 8'-substituted azafluorenones **2.380c** and **2.380d**.

Chapter 3 of this thesis describes an original approach to the synthesis of natural product isoprekinamycin, a member of the kinamycins family structurally characterized by the unusual diazobenzo[*b*]fluorene skeleton. This retrosynthetic plan heavily relied on the novel anionic *O*→α-vinyl carbamoyl translocation of 2-(*O*-carbamoyl) stilbenes discovered in our group (Scheme 3.17).[3] The synthesis of the key stilbene **3.113** was

efficiently achieved through exploitation of the solid nexus between large scale D*o*M and Suzuki-Miyaura cross coupling reaction. However, when exposed to LDA, **3.113** and its structural variations, all bearing methyl groups at $C_{2'}$ and/or C_6, underwent extensive decomposition which greatly eroded the yields of the desired 3-arylnaphthols (Table 3.3) thus determining a drastic modification of this approach to isoprekinamycin. After several attempts, an efficient route to naphthol **3.272** was devised thus providing an alternative access to the advanced intermediates (**3.274** and **3.278**, Schemes 3.55 and 3.56 respectively) which, based on the precedent described by Mohri,[4] were to undergo two consecutive DreM reactions. The first of these proved to be unusually challenging thus preventing the completion of this synthesis. Substrate modifications of **3.272** are now under active investigation in our lab in an attempt to elicit the desired DreM reactivity of this crucial intermediate.

More than twenty years ago, intermolecular competition studies carried out by Watanabe demonstrated that the $OPO(NMe_2)_2$ group displays a DMG power twice as high as that of the carbamate group.[5] At the same time, however, it exhibits a higher migratory aptitude than the latter imposing the use of temperatures as low as −105 °C in order to prevent the facile 1,3 *P*-Fries rearrangement. To test the hypothesis that a bulkier analog of the $OPO(NMe_2)_2$ group may retain a similar DMG power while displaying a better stability during metalation at higher temperatures, tetra*ethyl*phosphorodiamidate **4.126a,b** were prepared and subjected to *ortho*-lithiation at −78 and −30 °C. These tests demonstrated that the $OPO(NEt_2)_2$ group indeed completely resists 1,3 O→C migration at -78 °C but rapidly undergoes translocation to the *ortho*-position at -30 °C. An intermolecular competition experiment against diethyl phenyl carbamate showed that the directing

power of the $OPO(NEt_2)_2$ is comparable to that of the $OCONEt_2$ group. While exploring the chemistry available to this DMG, phosphorodiamidate (**4.127i**) was found capable of reacting according to the 1,4-vinylogous *P*-Fries rearrangement and furnishing phosphonamide **4.143** which is a valuable intermediate of the Corey olefination. The homologous 1,5-migration of the $OPO(NEt_2)_2$ group in biaryl and teraryls **4.154a,b** and **4.166a** has also been demonstrated to occur albeit in more drastic conditions, thus widening further the scope of this DMG.

5.2 References

[1] Krizan, T.D.; Martin, J.C. *J. Am. Chem. Soc.* **1983,** *105*, 6155-6157.

[2] Caron, S.; Hawkins, J.M. *J. Org. Chem.* **1998**, *63*, 2054-2055.

[3] Reed, M.A.; Chang, M.T.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2297-2300.

[4] Mohri, S.-i.; Stefinovich, M.; Snieckus, V. *J. Org. Chem.* **1997***, 62*, 7072-7073.

[5] Watanabe, M.; Date, M.; Kawanishi, K.; Hori, T.; Furukawa, S. *Chem. Pharm. Bull.* **1990**, *38*, 2637-2643. Watanabe, M.; Date, M.; Kawanishi, K.; Tsukazaki, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 2564-2566.

APPENDICES

Table 1. Crystal data and structure refinement for **2.184a**

Empirical formula	C32 H51 N O3 Si	
Formula weight	525.83	
Temperature	180(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 34.707(6) Å	α= 90°.
	b = 8.6680(15) Å	β= 92.245(3)°.
	c = 21.172(4) Å	γ = 90°.
Volume	6365(2) $Å^3$	
Z	8	
Density (calculated)	1.098 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	2304	
Crystal size	0.4 x 0.3 x 0.3 mm^3	
Theta range for data collection	1.93 to 28.31°.	
Index ranges	-45<=h<=44, -11<=k<=9, -27<=l<=28	
Reflections collected	21852	
Independent reflections	7348 [R(int) = 0.0215]	
Completeness to theta = 28.31°	92.7 %	
Absorption correction	Empirical (Brukre SADABS)	
Max. and min. transmission	1.0000 and 0.9232	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7348 / 0 / 538	
Goodness-of-fit on F^2	0.942	
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR2 = 0.0915	
R indices (all data)	R1 = 0.0660, wR2 = 0.1007	
Largest diff. peak and hole	0.277 and -0.223 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.184a.** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	450(1)	-408(1)	-621(1)	37(1)
Si(1)	963(1)	4284(1)	1991(1)	32(1)
O(1)	594(1)	2031(1)	-325(1)	42(1)
O(2)	968(1)	3224(1)	639(1)	34(1)
O(3)	1523(1)	-2565(1)	-202(1)	41(1)
C(1)	2120(1)	1715(4)	-2208(1)	77(1)
C(2)	1784(1)	931(2)	-1901(1)	48(1)
C(3)	1767(1)	1219(2)	-1196(1)	39(1)
C(4)	1422(1)	449(2)	-909(1)	35(1)
C(5)	1410(1)	634(2)	-188(1)	30(1)
C(6)	1023(1)	59(2)	85(1)	30(1)
C(7)	674(1)	624(2)	-307(1)	34(1)
C(8)	95(1)	122(2)	-958(1)	49(1)
C(9)	157(1)	479(3)	-1646(1)	68(1)
C(10)	542(1)	-2059(2)	-694(1)	41(1)
C(11)	383(1)	-3070(2)	-184(1)	54(1)
C(12)	988(1)	448(1)	784(1)	28(1)
C(13)	991(1)	-764(2)	1216(1)	34(1)
C(14)	977(1)	-523(2)	1858(1)	40(1)
C(15)	967(1)	976(2)	2086(1)	37(1)
C(16)	965(1)	2251(1)	1680(1)	31(1)
C(17)	971(1)	1957(1)	1028(1)	29(1)
C(18)	553(1)	5412(2)	1624(1)	41(1)
C(19)	175(1)	4573(4)	1562(2)	81(1)
C(20)	1434(1)	5220(2)	1829(1)	43(1)
C(21)	1781(1)	4402(3)	2133(2)	74(1)
C(22)	906(1)	4187(2)	2869(1)	43(1)
C(23)	919(1)	5756(2)	3199(1)	62(1)
C(24)	1748(1)	-139(1)	170(1)	30(1)
C(25)	2023(1)	710(2)	524(1)	35(1)
C(26)	2318(1)	-48(2)	872(1)	41(1)

C(27)	2348(1)	-1640(2)	879(1)	40(1)
C(28)	2083(1)	-2489(2)	521(1)	39(1)
C(29)	1790(1)	-1760(2)	169(1)	33(1)
C(30)	2015(1)	2455(2)	538(1)	48(1)
C(31)	2665(1)	-2438(3)	1265(1)	57(1)
C(32)	1550(1)	-4208(2)	-222(1)	54(1)

Table 3. Bond lengths [Å] and angles [°] for **2.184a**.

N(1)-C(7)	1.3450(17)
N(1)-C(8)	1.4720(19)
N(1)-C(10)	1.4762(18)
Si(1)-C(20)	1.8694(16)
Si(1)-C(18)	1.8706(16)
Si(1)-C(22)	1.8785(17)
Si(1)-C(16)	1.8814(13)
O(1)-C(7)	1.2506(16)
O(2)-C(17)	1.3724(15)
O(3)-C(29)	1.3819(17)
O(3)-C(32)	1.4280(18)
C(1)-C(2)	1.516(3)
C(2)-C(3)	1.516(2)
C(3)-C(4)	1.519(2)
C(4)-C(5)	1.538(2)
C(5)-C(24)	1.5262(18)
C(5)-C(6)	1.5649(19)
C(6)-C(7)	1.5201(19)
C(6)-C(12)	1.5275(18)
C(8)-C(9)	1.513(3)
C(10)-C(11)	1.512(2)
C(12)-C(13)	1.3914(18)
C(12)-C(17)	1.4087(17)
C(13)-C(14)	1.379(2)
C(14)-C(15)	1.3871(19)
C(15)-C(16)	1.4004(18)

C(16)-C(17)	1.4045(19)
C(18)-C(19)	1.500(3)
C(20)-C(21)	1.518(3)
C(22)-C(23)	1.529(2)
C(24)-C(25)	1.3991(19)
C(24)-C(29)	1.4124(18)
C(25)-C(26)	1.400(2)
C(25)-C(30)	1.513(2)
C(26)-C(27)	1.384(2)
C(27)-C(28)	1.383(2)
C(27)-C(31)	1.512(2)
C(28)-C(29)	1.387(2)

C(7)-N(1)-C(8)	119.31(13)
C(7)-N(1)-C(10)	124.92(13)
C(8)-N(1)-C(10)	115.64(13)
C(20)-Si(1)-C(18)	110.69(8)
C(20)-Si(1)-C(22)	109.16(9)
C(18)-Si(1)-C(22)	109.08(9)
C(20)-Si(1)-C(16)	109.11(7)
C(18)-Si(1)-C(16)	110.87(7)
C(22)-Si(1)-C(16)	107.87(7)
C(29)-O(3)-C(32)	118.49(13)
C(3)-C(2)-C(1)	114.11(18)
C(2)-C(3)-C(4)	112.60(14)
C(3)-C(4)-C(5)	113.80(12)
C(24)-C(5)-C(4)	113.44(11)
C(24)-C(5)-C(6)	109.38(11)
C(4)-C(5)-C(6)	112.91(11)
C(7)-C(6)-C(12)	111.52(11)
C(7)-C(6)-C(5)	111.89(11)
C(12)-C(6)-C(5)	112.85(11)
O(1)-C(7)-N(1)	120.64(13)
O(1)-C(7)-C(6)	120.10(12)
N(1)-C(7)-C(6)	119.24(12)
N(1)-C(8)-C(9)	112.56(15)

N(1)-C(10)-C(11)	113.58(14)
C(13)-C(12)-C(17)	117.40(12)
C(13)-C(12)-C(6)	118.11(11)
C(17)-C(12)-C(6)	124.43(11)
C(14)-C(13)-C(12)	122.27(12)
C(13)-C(14)-C(15)	119.14(13)
C(14)-C(15)-C(16)	121.70(14)
C(15)-C(16)-C(17)	117.43(12)
C(15)-C(16)-Si(1)	121.58(11)
C(17)-C(16)-Si(1)	120.98(9)
O(2)-C(17)-C(16)	116.40(11)
O(2)-C(17)-C(12)	121.55(12)
C(16)-C(17)-C(12)	122.05(11)
C(19)-C(18)-Si(1)	115.50(15)
C(21)-C(20)-Si(1)	113.85(14)
C(23)-C(22)-Si(1)	114.16(12)
C(25)-C(24)-C(29)	117.07(12)
C(25)-C(24)-C(5)	121.98(11)
C(29)-C(24)-C(5)	120.93(12)
C(24)-C(25)-C(26)	120.20(13)
C(24)-C(25)-C(30)	121.65(13)
C(26)-C(25)-C(30)	118.15(14)
C(27)-C(26)-C(25)	121.91(15)
C(28)-C(27)-C(26)	118.35(14)
C(28)-C(27)-C(31)	120.54(16)
C(26)-C(27)-C(31)	121.11(17)
C(27)-C(28)-C(29)	120.65(13)
O(3)-C(29)-C(28)	122.42(12)
O(3)-C(29)-C(24)	115.80(12)
C(28)-C(29)-C(24)	121.78(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2.184a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	29(1)	48(1)	35(1)	-10(1)	-1(1)	0(1)
Si(1)	36(1)	27(1)	32(1)	-2(1)	3(1)	-3(1)
O(1)	40(1)	41(1)	44(1)	-4(1)	-7(1)	9(1)
O(2)	44(1)	26(1)	32(1)	3(1)	2(1)	0(1)
O(3)	46(1)	27(1)	50(1)	-5(1)	-2(1)	4(1)
C(1)	59(1)	118(2)	54(2)	28(2)	18(1)	8(1)
C(2)	41(1)	66(1)	38(1)	10(1)	4(1)	13(1)
C(3)	34(1)	43(1)	39(1)	7(1)	2(1)	5(1)
C(4)	33(1)	38(1)	34(1)	1(1)	1(1)	3(1)
C(5)	29(1)	26(1)	34(1)	0(1)	1(1)	3(1)
C(6)	30(1)	27(1)	34(1)	-3(1)	1(1)	1(1)
C(7)	29(1)	41(1)	31(1)	-4(1)	5(1)	2(1)
C(8)	30(1)	67(1)	48(1)	-18(1)	-6(1)	5(1)
C(9)	58(1)	89(2)	56(1)	4(1)	-15(1)	11(1)
C(10)	36(1)	47(1)	41(1)	-16(1)	3(1)	-4(1)
C(11)	58(1)	53(1)	52(1)	-8(1)	5(1)	-9(1)
C(12)	24(1)	29(1)	32(1)	-1(1)	1(1)	-1(1)
C(13)	36(1)	25(1)	41(1)	-2(1)	-1(1)	-2(1)
C(14)	53(1)	28(1)	37(1)	7(1)	-2(1)	-4(1)
C(15)	49(1)	34(1)	30(1)	1(1)	1(1)	-3(1)
C(16)	33(1)	27(1)	34(1)	0(1)	2(1)	-2(1)
C(17)	27(1)	26(1)	33(1)	3(1)	3(1)	-1(1)
C(18)	44(1)	33(1)	47(1)	-5(1)	-1(1)	1(1)
C(19)	43(1)	86(2)	111(2)	18(2)	-23(1)	-12(1)
C(20)	40(1)	40(1)	48(1)	-7(1)	7(1)	-7(1)
C(21)	40(1)	75(2)	106(2)	-12(1)	-5(1)	2(1)
C(22)	55(1)	39(1)	37(1)	-3(1)	5(1)	-4(1)
C(23)	92(2)	54(1)	41(1)	-14(1)	12(1)	-5(1)
C(24)	28(1)	32(1)	30(1)	1(1)	4(1)	4(1)
C(25)	31(1)	38(1)	37(1)	-1(1)	3(1)	4(1)
C(26)	34(1)	52(1)	38(1)	-5(1)	-2(1)	5(1)

C(27)	37(1)	53(1)	33(1)	6(1)	7(1)	16(1)
C(28)	44(1)	36(1)	38(1)	6(1)	8(1)	13(1)
C(29)	35(1)	33(1)	32(1)	0(1)	6(1)	5(1)
C(30)	40(1)	38(1)	64(1)	-8(1)	-9(1)	-1(1)
C(31)	51(1)	76(1)	45(1)	11(1)	0(1)	27(1)
C(32)	69(1)	28(1)	65(1)	-2(1)	1(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2.184a**.

	x	y	z	U(eq)
H(2)	851(5)	2930(20)	279(9)	64(6)
H(1B)	2358(7)	1270(20)	-2023(11)	97(7)
H(1A)	2118(6)	1420(20)	-2652(12)	90(7)
H(1C)	2114(7)	2820(30)	-2149(12)	116(10)
H(2B)	1553(5)	1269(17)	-2109(7)	48(4)
H(2A)	1790(5)	-190(20)	-1980(8)	57(5)
H(3B)	2010(4)	839(14)	-983(7)	34(4)
H(3A)	1762(4)	2332(17)	-1113(7)	42(4)
H(4B)	1429(4)	-604(17)	-1022(7)	46(4)
H(4A)	1176(4)	879(15)	-1104(7)	38(4)
H(5)	1426(4)	1723(15)	-101(6)	25(3)
H(6)	1026(4)	-1030(14)	69(6)	23(3)
H(8A)	-1(5)	1072(19)	-750(8)	59(5)
H(8B)	-89(5)	-686(19)	-931(8)	56(5)
H(9A)	-77(6)	830(19)	-1857(9)	69(6)
H(9B)	256(6)	-490(20)	-1861(10)	85(7)
H(9C)	352(7)	1250(30)	-1707(10)	98(8)
H(10B)	821(5)	-2179(15)	-721(6)	36(4)
H(10A)	435(4)	-2351(15)	-1098(7)	38(4)
H(11C)	100(6)	-2891(19)	-174(8)	64(5)
H(11B)	440(6)	-4140(20)	-286(9)	75(6)
H(11A)	492(5)	-2790(20)	232(10)	72(6)

H(13)	1002(4)	-1794(15)	1060(6)	31(3)
H(14)	979(4)	-1381(17)	2151(7)	44(4)
H(15)	964(4)	1142(14)	2526(7)	29(4)
H(18A)	528(6)	6320(20)	1852(9)	77(6)
H(18B)	621(5)	5678(18)	1206(9)	64(6)
H(19A)	-42(6)	5230(20)	1384(9)	79(6)
H(19C)	166(12)	3650(50)	1410(20)	210(20)
H(19B)	98(7)	4270(30)	1961(13)	111(10)
H(20A)	1439(5)	6260(20)	1965(8)	62(5)
H(20C)	1456(5)	5220(18)	1379(8)	56(5)
H(21A)	2019(7)	4840(20)	2019(9)	85(7)
H(21B)	1797(6)	3330(30)	2001(10)	92(7)
H(21C)	1760(6)	4430(20)	2609(11)	84(7)
H(22B)	1091(5)	3503(18)	3068(8)	55(5)
H(22A)	663(5)	3710(19)	2936(8)	59(5)
H(23A)	862(5)	5718(19)	3642(10)	72(6)
H(23B)	1182(7)	6210(20)	3176(10)	94(8)
H(23C)	715(6)	6500(20)	3012(9)	73(6)
H(26)	2493(4)	574(16)	1112(7)	45(4)
H(28)	2103(4)	-3565(18)	516(7)	43(4)
H(3OB)	1763(5)	2829(18)	694(8)	56(5)
H(30A)	2040(5)	2897(18)	91(9)	61(5)
H(30C)	2224(6)	2857(19)	831(9)	65(5)
H(31A)	2577(6)	-3040(20)	1566(11)	91(8)
H(31B)	2844(7)	-2900(20)	999(10)	87(7)
H(31C)	2819(8)	-1740(30)	1491(14)	132(11)
H(32A)	1814(6)	-4527(19)	-339(8)	62(5)
H(32B)	1508(5)	-4630(20)	199(10)	69(6)
H(32C)	1347(6)	-4520(20)	-527(9)	71(6)

Table 6. Torsion angles [°] for **2.184a**.

C(1)-C(2)-C(3)-C(4)	178.60(17)
C(2)-C(3)-C(4)-C(5)	176.37(13)
C(3)-C(4)-C(5)-C(24)	-63.72(16)
C(3)-C(4)-C(5)-C(6)	171.12(12)
C(24)-C(5)-C(6)-C(7)	-172.55(11)
C(4)-C(5)-C(6)-C(7)	-45.22(15)
C(24)-C(5)-C(6)-C(12)	60.71(14)
C(4)-C(5)-C(6)-C(12)	-171.97(11)
C(8)-N(1)-C(7)-O(1)	-3.5(2)
C(10)-N(1)-C(7)-O(1)	172.32(14)
C(8)-N(1)-C(7)-C(6)	175.08(13)
C(10)-N(1)-C(7)-C(6)	-9.1(2)
C(12)-C(6)-C(7)-O(1)	60.62(17)
C(5)-C(6)-C(7)-O(1)	-66.83(16)
C(12)-C(6)-C(7)-N(1)	-118.00(13)
C(5)-C(6)-C(7)-N(1)	114.54(13)
C(7)-N(1)-C(8)-C(9)	93.66(19)
C(10)-N(1)-C(8)-C(9)	-82.6(2)
C(7)-N(1)-C(10)-C(11)	91.86(19)
C(8)-N(1)-C(10)-C(11)	-92.15(18)
C(7)-C(6)-C(12)-C(13)	120.19(13)
C(5)-C(6)-C(12)-C(13)	-112.88(13)
C(7)-C(6)-C(12)-C(17)	-62.78(17)
C(5)-C(6)-C(12)-C(17)	64.16(16)
C(17)-C(12)-C(13)-C(14)	0.1(2)
C(6)-C(12)-C(13)-C(14)	177.31(13)
C(12)-C(13)-C(14)-C(15)	-1.2(2)
C(13)-C(14)-C(15)-C(16)	1.1(2)
C(14)-C(15)-C(16)-C(17)	0.2(2)
C(14)-C(15)-C(16)-Si(1)	-178.55(12)
C(20)-Si(1)-C(16)-C(15)	111.84(13)
C(18)-Si(1)-C(16)-C(15)	-126.00(13)
C(22)-Si(1)-C(16)-C(15)	-6.63(15)
C(20)-Si(1)-C(16)-C(17)	-66.84(13)

C(18)-Si(1)-C(16)-C(17)	55.32(14)
C(22)-Si(1)-C(16)-C(17)	174.69(12)
C(15)-C(16)-C(17)-O(2)	179.87(12)
Si(1)-C(16)-C(17)-O(2)	-1.40(17)
C(15)-C(16)-C(17)-C(12)	-1.4(2)
Si(1)-C(16)-C(17)-C(12)	177.38(10)
C(13)-C(12)-C(17)-O(2)	179.96(12)
C(6)-C(12)-C(17)-O(2)	2.9(2)
C(13)-C(12)-C(17)-C(16)	1.2(2)
C(6)-C(12)-C(17)-C(16)	-175.82(12)
C(20)-Si(1)-C(18)-C(19)	163.6(2)
C(22)-Si(1)-C(18)-C(19)	-76.3(2)
C(16)-Si(1)-C(18)-C(19)	42.4(2)
C(18)-Si(1)-C(20)-C(21)	177.90(16)
C(22)-Si(1)-C(20)-C(21)	57.83(17)
C(16)-Si(1)-C(20)-C(21)	-59.83(17)
C(20)-Si(1)-C(22)-C(23)	58.69(18)
C(18)-Si(1)-C(22)-C(23)	-62.37(18)
C(16)-Si(1)-C(22)-C(23)	177.12(16)
C(4)-C(5)-C(24)-C(25)	115.26(14)
C(6)-C(5)-C(24)-C(25)	-117.71(14)
C(4)-C(5)-C(24)-C(29)	-66.28(17)
C(6)-C(5)-C(24)-C(29)	60.75(16)
C(29)-C(24)-C(25)-C(26)	-1.8(2)
C(5)-C(24)-C(25)-C(26)	176.74(13)
C(29)-C(24)-C(25)-C(30)	177.51(15)
C(5)-C(24)-C(25)-C(30)	-4.0(2)
C(24)-C(25)-C(26)-C(27)	0.0(2)
C(30)-C(25)-C(26)-C(27)	-179.27(16)
C(25)-C(26)-C(27)-C(28)	1.3(2)
C(25)-C(26)-C(27)-C(31)	-179.11(16)
C(26)-C(27)-C(28)-C(29)	-0.8(2)
C(31)-C(27)-C(28)-C(29)	179.58(16)
C(32)-O(3)-C(29)-C(28)	0.2(2)
C(32)-O(3)-C(29)-C(24)	-179.85(15)
C(27)-C(28)-C(29)-O(3)	178.99(13)

C(27)-C(28)-C(29)-C(24)	-1.0(2)
C(25)-C(24)-C(29)-O(3)	-177.71(12)
C(5)-C(24)-C(29)-O(3)	3.76(19)
C(25)-C(24)-C(29)-C(28)	2.3(2)
C(5)-C(24)-C(29)-C(28)	-176.27(13)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **2.184a** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(1)	0.884(19)	1.718(19)	2.5890(15)	167.7(17)

Symmetry transformations used to generate equivalent atoms: