I. PROGRESS IN DIRECTED *ortho* METALATION

AND

II. GENERATING CHIRALITY IN PERIODIC MESOPOROUS ORGANOSILICA

by

Tom Blackburn

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Abstract

Chapter 1 constitutes a review of current methods of aromatic substitution focusing on Directed *ortho* Metalation (D*o*M) and Directed *remote* Metalation (D*re*M). The field of mesoporous silica is reviewed in Chapter 2, focusing on the preparation, characterization, and application of mesoporous silicates.

Chapter 3 presents an introduction of phosphorus based Directed Metalation Groups (DMGs). The development of the directed ortho metalation (DoM) reaction of the tetraethyl phosphorodiamidate DMG is described. In addition to being one of the most powerful DMGs, migration of the $OPO(NEt_2)_2$ group to the *ortho* and *remote* positions is demonstrated, constituting new reactions as well as affording new organophosphorus compounds.

Attempts to improve the synthetic utility of the DMG led to the discovery and optimization of a two new nickel-catalyzed cross coupling reactions, which is described in Chapter 4. Both the $OPO(NEt_2)_2$ and $OCONEt_2$ DMGs are demonstrated to undergo cross coupling reactions with aryl boronic acids.

By means of D*o*M and cross coupling tactics, the concise synthesis of a chiral binaphthol bridged silasesquioxane is described. Chapter 5 explores new methods to prepare chiral periodic mesoporous organosilica (PMO) materials using this monomer. PMOs are prepared by the co-condensation of a relatively small amount of chiral binaphthyl dopant which acts to twist the bulk prochiral biphenylene framework.

Acknowledgements

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List of Abbreviations

Å	Ångstrom
acac	acetylacetonyl
AIBN	2,2'-azo *bis*isobutyronitrile
APTES	aminopropyl triethoxysilane
BET	Brunauer-Emmett-Teller
BJH	Barrett-Joyner-Halenda
BINOL	1,1'-bi-2,2'-naphthol
Boc	*t*-Butoxycarbonyl
Bpy	2,2'-bipyridyl
CD	circular dichroism
CIPE	complex-induced proximity effect
COD	1,5-cyclooctadiene
CTAB	cetyl trimethyl ammonium bromide
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
dba	dibenzylideneacetone
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
ee	enantiomeric excess
Et	ethyl
EVL	ethoxyvinyllithium
EWG	electron-withdrawing group
FG	functional group
gCOSY	gradient-selected correlation spectroscopy
GSH	glutathione
F127	Pluronic F127
h	hours
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
^{i}Pr	isopropyl
Ipr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared
IUPAC	International Union of Pure and Applied Chemists
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
MAS	magic angle spinning
MCM	Mobil composition of matter
Me	methyl
Mes	2,4,6-trimethylbenzene
MNDO	modified-neglect of diatomic overlaps
MOM	methoxymethyl
MPTMS	mercaptopropyl trimethoxysilane
Ms	mesyl (methanesulfonyl)
M-X	metal-halogen exchange
NBS	*N*-bromosuccinimide
NOESY	nuclear Overhauser enhancement spectroscopy
OAm	N,N-diethylcarbamate
OPAm	*N*,*N*,*N*',*N*'-Tetraethylphosphorodiamidate
P123	Pluronics P123
PEG	poly ethylene glycol
PG	protecting group
PM3	parametric method 3
PMB	*p*-methoxybenzyl
PMDTA	*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine
PMO	periodic mesoporous organosilica
PPA	polyphosphoric acid
PTSA	*p*-toluene sulfonic acid
Q_n	silicon bearing 4 oxygen and n Si-O-Si linkages

RCM	ring closing metathesis
SBA	Santa Barbara amorphous type material
SEM	scanning electron microscopy
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	*t*-butyldimethylsilyl
TEDI	1,1,3,3,-tetraethyl-1,3-disilaisoindolines
TEM	transmission electron microscopy
TEOS	tetraethylorthosilicate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFP	*tris*(2-furyl)phosphine
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
TMCDA	*N*,*N*,*N*',*N*'-tetramethy-1,2-diaminocyclohexane
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMB	1,3,5 trimethylbenzene
TMOS	tetramethylorthosilicate
TMS	trimethylsilyl
TS	transition state
Ts	*p*-toluenesulfonyl
XRD	X-ray diffraction

Chapter 1

General Introduction

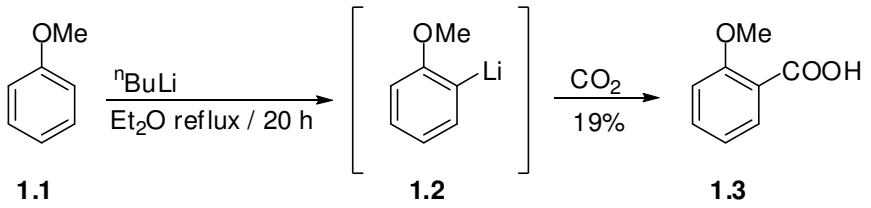
1.1 The Synthesis of Aromatic Compounds

Aromatic compounds constitute approximately one third of the worldwide organic chemical production.[1a] The importance of aromatic molecules as drug entities[2] accounts for a large portion of this production. The regioselective preparation of functionalized aromatics is therefore an ongoing significant endeavor. Electrophilic aromatic substitution (EAS)[1] is the traditional method but in many cases is not ideal. Reaction conditions are typically harsh and, although substitution is "directed" by given substituents, regioselectivity is generally poor. As a result, methods such as (SNAr)[3] and (SNR1),[4] Directed ortho Metalation (DoM),[5] and more recently transition metal catalyzed reactions[6] have succeeded where EAS fails or is impractical.

1.2 Directed *Ortho* Metalation (D*o*M)

The origin of the D*o*M reaction began with two independent discoveries by Gilman[7] and Wittig.[8] These workers demonstrated that anisole **1.1** undergoes an *ortho*-deprotonation in the presence of ^{n}BuLi, to give the suggested anionic intermediate **1.2** since quench with carbon dioxide afforded 2-methoxybenzoic acid in 19% yield (Scheme 1.1). Although initial yields were low, the high regioselectivity invoked interest and as a result the D*o*M reaction evolved into a truly general synthetic methodology.[9] Today the methodology continues to improve, new Directed Metalation Groups (DMGs) are being

developed, mechanistic aspects are becoming more apparent, and its further use is greatly increasing by industry.[10] Since extensive reviews are available,[5] discussion will be limited to common DMGs, mechanistic aspects, advances in the field, connections, and complementarities of D*o*M to other methodologies.



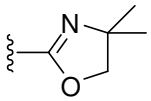
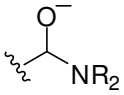
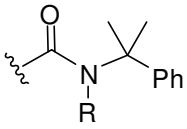
Scheme 1.1 The Directed *ortho* Metalation Reaction.

1.3 Directed Metalation Groups (DMGs)

The question posed by the Gilman and Wittig discovery is why does anisole undergo deprotonation whereas benzene is relatively unreactive towards ^{n}BuLi? [11] Clearly, the methoxy group must play a role, therefore the difference in anisoles reactivity was attributed to the ability of the methoxy group to coordinate the alkyllithium and hold it in close proximity to the *ortho* proton.[12] As the DoM reaction evolved, the major features for the success of the reaction became recognized: DMGs must include a heteroatom for coordination purposes which, arguably, can coordinatively deprotonate via a 5-membered ring transition state (or intermediate). It can be shown that the power of a directing group is a feature related to its coordination ability and is determined through inter- and intramolecular competition studies [5a,13] It is important to note that these studies are done under kinetic control and should be taken as qualitative. DMGs also must be sufficiently resistant to nucleophilic attack either by electronic or steric

considerations. DMGs are formally grouped in two classes, carbon and heteroatom based, referring to the atom which directly connects the DMG to the aromatic ring (Table 1.1).[14]

Table 1.1 Selected Directed Metalation Groups.

Carbon-Based DMGs		Ref.	Heteroatom-Based DMGs		Ref.
CONHR	Hauser, 1964	13a	SO_2NHR	Hauser, 1968	13h
	Meyers, 1975 Gschwend, 1975	13b 13c	SO_2NR_2 OCH_2OCH_3	Hauser, 1969 Christensen, 1975	13i 13j
$CONEt_2$	Beak, 1977	13d	$NHCO^tBu$	Gschwend, 1979	13k
	Comins, 1982*	13e	$NHCOO^tBu$ $OCONEt_2$	Muchoswki, 1980 Snieckus, 1983	13l 13m
COOH	Mortier, 1994	13f	$P(O)(^tBu)_2$	Snieckus, 1998	13n
	Snieckus, 1999	13g	OSO_2NR_2 $OCON(TMS)^iPr$	Snieckus, 2003 Hoppe, 2006*	13o 13p

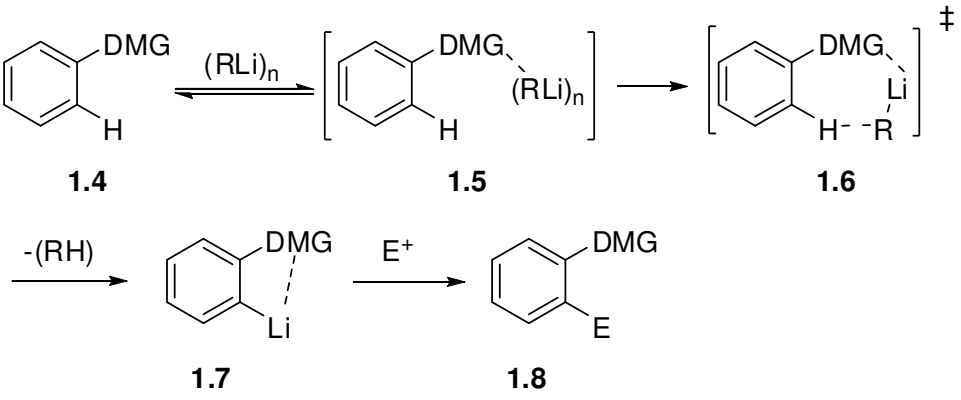
* Generated *in situ*.

The synthetic utility of a DMG is not just determined by its directing strength but its ability for further conversion to other functional groups, which is not always trivial because many DMGs by design are highly resistant to nucleophilic attack. However DMGs such as oxazolines provide access to carboxylic acids, OMOM, and NHBoc groups are relatively easily hydrolyzed to give phenols and anilines respectively.[15a,b] The powerful tertiary amide DMGs has proven difficult to hydrolyze; however cumyl amides offers an attractive partial option since it may be decumylated with ease to the more readily manipulated primary amides.[13g] Similarly *N*-TMS-*N*-isopropyl carbamates[14p] may be mildly cleaved hydrolytically to phenol. Aromatic aldehydes may be converted *in situ*

to α-amino alkoxides, which serve as useful DMGs, and then converted back to the aldehydes upon aqueous work up.[16] diethyl-sulfonamides,[17] sulfamates[13o] and carbamates[18] have been demonstrated to undergo cross coupling with organomagnesium reagents under Ni(0) catalysis (Kumada-Corriu reaction). Similarly utilizing ^{i}PrMgBr as a hydride source, both the SO_2NEt_2 and $OCONEt_2$ groups, may be reductively cleaved making them valuable latent DMGs.[16,187] The Schwartz reagent, a zirconium hydride, has been shown to reduce tertiary amides and more recently carbamates[19] under relatively mild conditions.

1.4 Mechanism

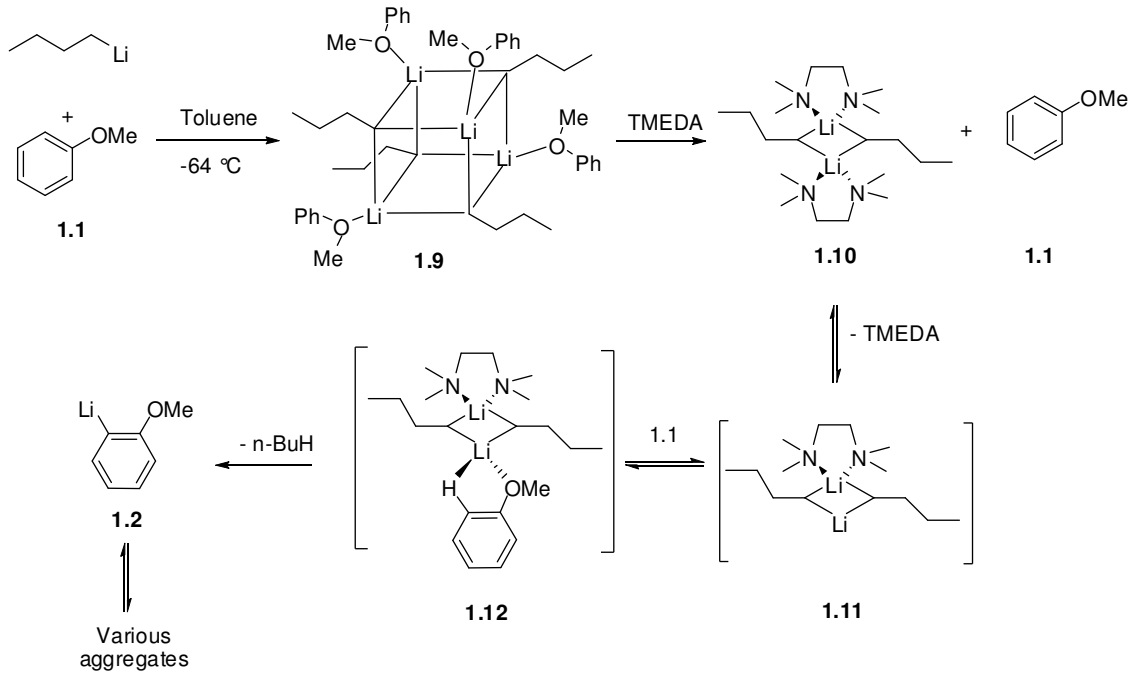
There is no unifying mechanism for the D*o*M reaction that can explain all the subtleties observed experimentally. For many DMG substrates there is no explanation to the observed effects of solvent, base, additives, and order of addition. The most widely accepted mechanism of D*o*M however can be summarized in 3 steps (Scheme 1.2).



Scheme 1.2 The CIPE Mechanism.

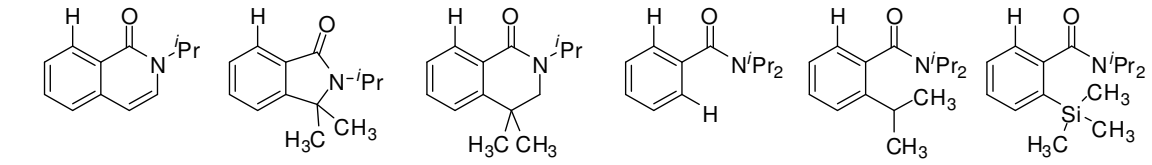
A rapid equilibrium between alkyllithium aggregates and a prelithiation complex of the alkyllithium coordinated to the DMG **1.5**. It is this complex in which the base is in close proximity to the *ortho* proton which allows the slow but irreversible proton abstraction forming the coordinated *ortho*-lithiated species **1.7**. Addition of a suitable electrophile provides in the simplest cases the regioselective formation of a 1,2-disubstituted arene **1.8**. The initial hypothesis for this mechanism was first proposed by Beak and Myers,[20] and later by Klumpp,[21] and was dubbed by the former chemists as the complex-induced proximity effect (CIPE).

Although some experimental observations support this mechanistic hypothesis, irrefutable evidence is as yet not available. Amongst the kinetic data supporting the prelithiation[22] complex Beak provided a study on the metalation of *N*,*N*,-dialkylbenzamides. Reaction monitoring by stopped-flow FT-IR spectroscopy[23] revealed the presence of prelithiated complexes but ruled out the involvement of any single complex. In a detailed NMR study,[24] Schleyer and coworkers observed the coordinated prelithiation complex via ^{7}Li and ^{1}H HOESY upon the metalation of anisole with ^{n}BuLi in a hydrocarbon solvent (Scheme 1.3). A strong coordination ^{n}BuLi-OMe complex **1.9** was observed which; was found to be unproductive and, upon the addition of TMEDA, underwent dissociation and disaggregation to form the species **1.10**.[25] The existence of the species **1.2** is confirmed by experimental evidence, and several crystal structures of aggregates.[26]



Scheme 1.3 Alkyllithium Aggregates in Hydrocarbon Solvents.

Other results offer inferential proof for CIPE. Thus in a competitive *ortho* lithiation study of structurally related amides, it has been shown that a DMG's efficiency increases as the dihedral angle between the *ortho*-proton and the carbonyl group decreases. This supports the hypothesis that proximity of the carbonyl oxygen lone pairs to which the base coordinates to and the *ortho* proton is critical for effective lithiation (Figure. 1.1).[27]

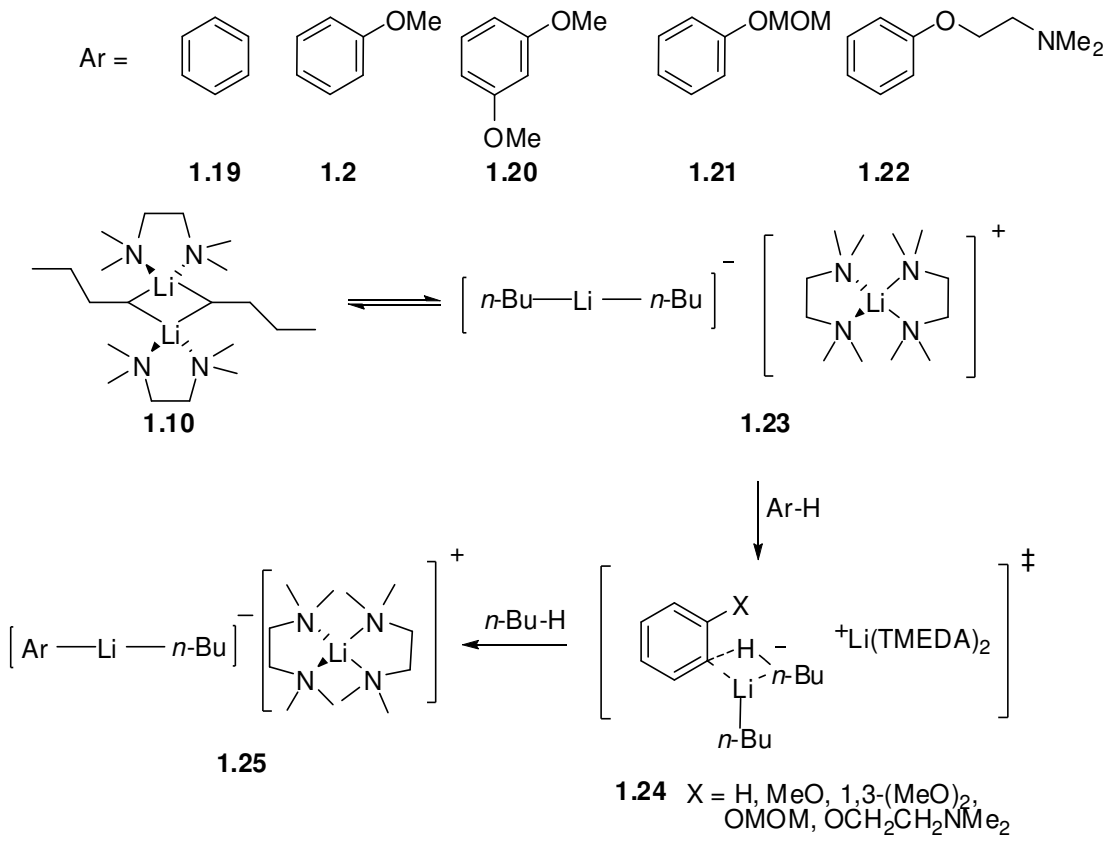


1.13	1.14	1.15	1.16	117	1.18
32000 (0)	6400 (1)	2500 (13)	1800 (57)	57 (91)	1 (103)

competitive efficiency (dihedral angle, deg)

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

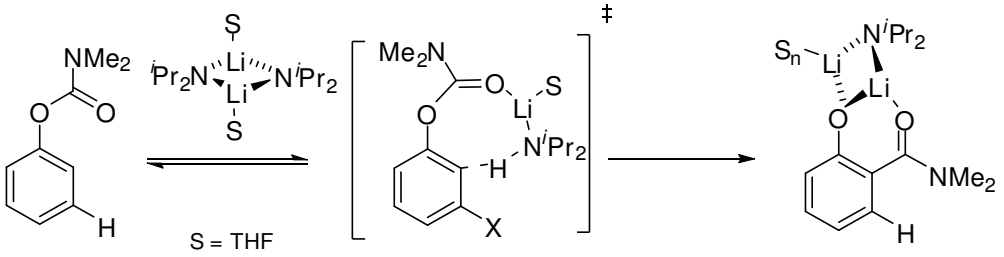
More recently, Collum has provided a series of systematic studies on the mechanism of D*o*M.[28] The role of TMEDA has been examined in a kinetic study of the *ortho* metalation of five aromatic substrates (Scheme 1.4). [27b] To account for the five substituent-dependent rates, a single substrate-independent mechanism is obligatory, with a transition state of the following stoichiometry: $[(^{n}BuLi)_2(TMEDA)_2(Ar\text{-}H)]^{\ddagger}$. Collum reasoned that a common transition state that can explain the *ortho* lithiation of substrates with such a large difference in coordinative ability must not be heavily dependent on Li-O complexation. Hence the regioselectivity of lithiation must be dependent on other factors such as inductive effects of the ring. A triple ion **1.24** model transition state was proposed for which evidence computational and crystallographic data.[29]



Scheme 1.4 The Triple Ion Model.

The conclusions from the above study cannot be extended to many of DMGs that are more strongly coordinating such as the carboxamide. Probing further, Collum investigated the anionic Snieckus-Fries rearrangement of aryl *O*-carbamates bearing various *meta*-substituents (Scheme 1.5) using React IR and NMR techniques. Kinetic data and observed precomplexes[30] indicate, that *ortho* lithiation of **1.26** is the rate limiting step which is followed by the rapid anionic *ortho* Fries rearrangement to **1.28**. From the kinetic data the rate law (eqn.1) was derived which is consistent with a mechanism involving the monomeric-based transition state **1.27** (Scheme 1.5).

$$-d[\mathbf{1.26}]/dt = k'[\mathbf{1.26}][\mathrm{LDA}]^{1/2}[\mathrm{THF}]^{0} \qquad \text{(eqn. 1)}$$

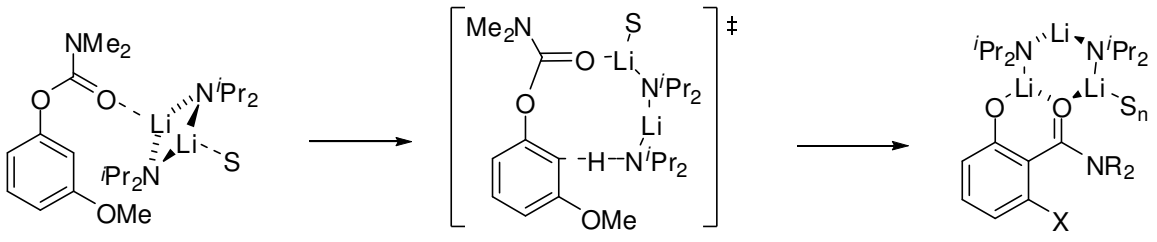


1.26 **1.27** **1.28**

Scheme 1.5 Monomeric Transition State of D*o*M in THF.

In contrast, the *m*-methoxy *O*-carbamate precomplex **1.29** was observed to quantitatively form in poorly coordinating solvents such as ^{t}BuOMe and ^{n}BuOMe and to be converted into complex **1.31** following the rate law (eqn.2) which is consistent with this reaction proceeding via the dimer transition state **1.30** (Scheme 1.6). The marked changes in the concentration dependencies is a consequence of the initial LDA-arene complex **1.29**; however, the emergence of dimer-based reactivity represents a fundamental change in mechanism associated with the change to a poorly coordinating solvent.

$$-d[\mathbf{1.29}]/dt = k'[\mathbf{1.29}][\mathrm{LDA}]^{0}[^{n}\mathrm{BuOMe}]^{0} \qquad \text{(eqn 2)}$$

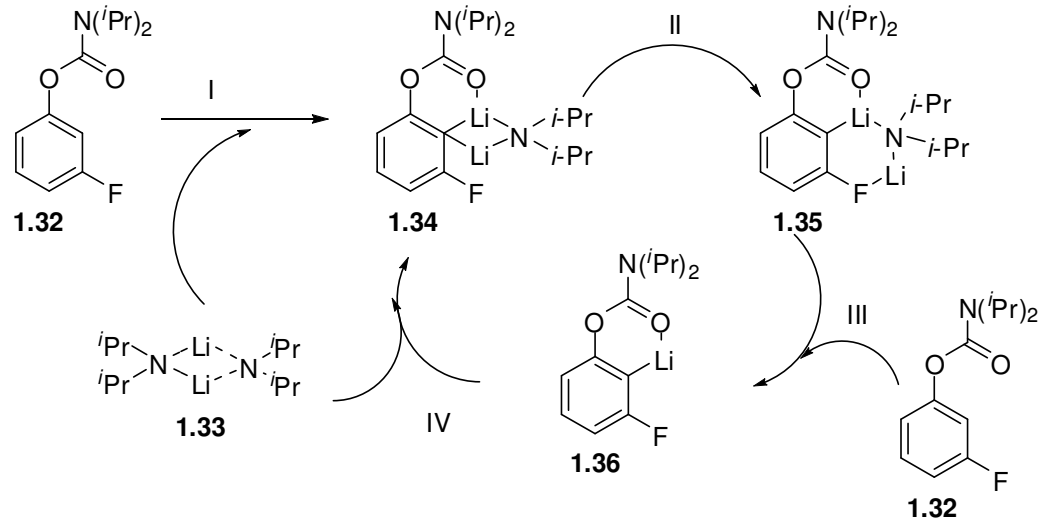


1.29 S = ^{n}BuOMe **1.30** **1.31**

Scheme 1.6 Dimeric Transition State of D*o*M in ^{n}BuOMe.

Collum has further examined the LDA mediated Snieckus-Fries rearrangement[31] of the *m*-fluoro *O*-carbamates **1.32** and has found it to be the most mechanistically complex reaction with LDA (Scheme 1.7). It was found that autocatalysis (**step III**) results from the intervening LDA-ArLi mixed dimers **1.34** and **1.35**. Metalation of the arene **1.32** by minor isomer **1.35** (**step III**) is an important step in this unusual autocatalysis; however, it is the condensation of aryllithium **1.37** with LDA dimer **1.33** (**step IV**) which is rate limiting.

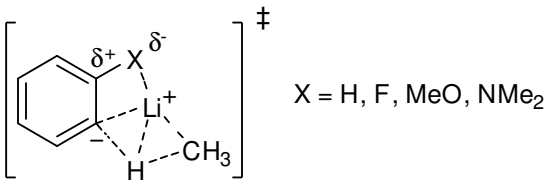
In additional studies of solvent effects on the Snieckus-Fries rearrangement. [30a] Collum showed that strongly coordinating solvents such as HMPA and TMCDA promote the formation of reactive monomeric lithiated intermediates while weakly coordinating Me_2NEt and strongly coordinating yet hindered TMEDA give mixtures of mixed-dimers and trimers.



Scheme 1.7 Autocatalysis of Carbamates with LDA.

The close examination of many organolithium reactions has led to some surprising discoveries which have baffled many chemists in the past. Most investigators prepare ^{n}BuLi *in situ* or obtain it from commercial sources, likewise with LDA. In many cases unpurified ^{n}BuLi or LDA can contain varying amounts of LiCl or other lithium salts which can lead to $>10^2$ swings in reaction rates. Collum has recently found that LiCl and other salts of lithium have shown tremendous rate acceleration from as little as 0.5% additions.[32] The greatest rate accelerations are found with moderately coordinating DMGs, most notably halogens, which may foreshadow results of ongoing mechanistic studies; LiCl catalysis however does not affect regioselectivity of metalation.

Prior to Collum's work, Schleyer[23] postulated that if a weakly bound complex existed in equilibrium, it should leave the majority of the substrate uncoordinated and thus free to undergo reaction with little selectivity. Indeed, the presence of a tightly bound complex would imply the requirement of a higher activation energy being required, thus lowering reactivity. For these reasons, Schleyer proposed a four centered transition state as the sole event (Figure. 1.2).[33]



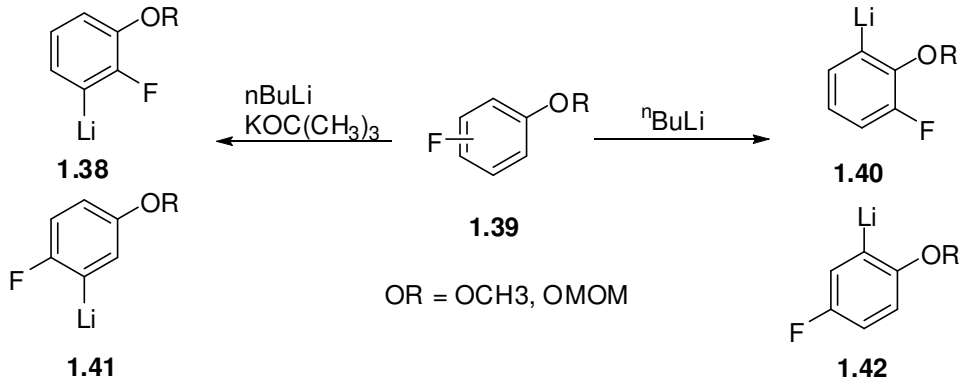
1.37

Figure 1.2 Postulated Four-Center Transition State.

Schleyer proposed that the strong stabilization of the four-center transition state is responsible for the directing and accelerating effects of the DMG, for which introduced

the term "kinetically enhanced metalation". This postulate is based on the fact that halogens such as fluorine,[34,35] chlorine,[36] and CF_3[37,38] act as moderate DMGs but are not highly coordinating. It is proposed that activation of the arene occurs via inductive effects (acidifying *ortho* hydrogens) and stabilization of charge. High level calculations seem to support this transition state **1.38**, placing the coordinating heteroatom and lithium in plane with the aromatic ring.

Inductive effects have been used to explain the sometimes switchable regioselectivities observed as a function of bases and additives. Schlosser[39] demonstrated that regioselectivity changes in the deprotonation of **1.39** and **1.40** when ^{n}BuLi precomplexed with potassium *tert*-butoxide, similar effects were observed with *N,N,N',N'',N''*-pentamethyldiethylenetriamine (Scheme 1.8).[40]



Scheme 1.8 Change in Regioselectivity with Fluoro-Anisoles.

Similar effects have been demonstrated by Mortier[41] on methoxy benzoic acids. The tunable selectivity is rationalized in that weakly solvated organolithium reagents preferentially coordinate to strong DMGs and undergo reaction via CIPE, whereas a fully complexed base (^{t}BuOK or PMDTA) does not compete for coordination by DMGs and

undergo reaction selectively at positions where negative charge is most effectively stabilized.[42]

The KEM postulate of Schleyer is a rationalization of regioselectivity according to inductive effects and supported by calculations only. The CIPE-based mechanism is based on considerable experimental evidence and is strengthened by the precomplex being spectroscopically observed. Interestingly, Collum has shown[28-32] that the critical factors seem to depend on the energetic cost of desolvation rather than precomplexation. In summary the D*o*M reaction is a multifaceted event, displaying complex kinetics, solvent and additive effects, and, in the case of the $OCONR_2$ DMG unique autocatalysis for which, to date, a unifying mechanism has not been presented to support all experimental evidence.

1.5 Bases for the D*o*M Reaction

The widespread use of the D*o*M reaction has led to the development of numerous synthetic protocols. Alkyllithiums with pKa in the range of (34-53) have been used extensively in conjunction with a variety of ligands such as TMEDA to break down aggregates.[43,29] The use of lithium amide bases are, especially LDA (pKa= 36) and LiTMP (pka =38) is common for substrates with potential to undergo rearrangement, self -condensation, or contain incompatible function groups that are susceptible to nucleophilic attack or undergo metal-halogen or proton exchange reactions with alkyl lithium's. Metalation is now commonly done in the presence of halogens and π-deficient heteroaromatics. Recently, the need for further improvement of functional group

tolerance and less reliance on cryogenic temperatures has led to the development of non-lithium organometallic bases.

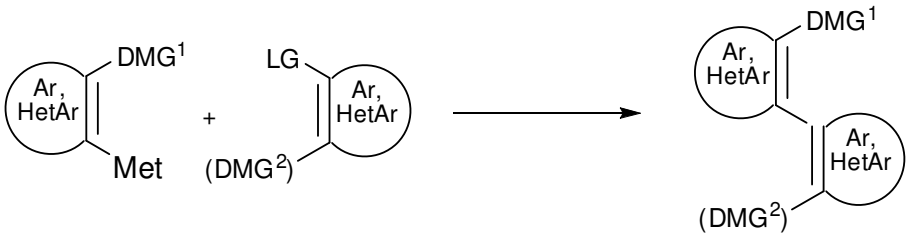
Organomagnesate's first employed by Wittig,[44] and several mixed Li/Mg bases have been used in D*o*M and have proven to be exceeding useful in D*o*M.[45,46,47] Knochel has recently shown the use of the Mg/Li amines TMPMgCl•LiCl[48] and $(TMP)_2Mg$•2LiCl[49] which display fair solubility in THF and high functional group tolerance are useful for deprotonation of π-deficient heteroaryl substrates,[46a] electron-poor arenes bearing halogens, and the OC(O)O^{t}Bu DMG. [48b] The use of Knochel's mixed Mg/Li bases allows a wider selection of electrophiles through direct quench or through prior transmetalation of the arylmagnesiated intermediate with CuCN•2LiCl or $ZnCl_2$.[46-48] Aluminum bases such as $^i Bu_3Al(TMP)Li$[50] and the TMP-zincate TMP-Zn$^t Bu_2Li$[51] have been used for the metalation of arenes with sensitive functional groups. Although these methodologies are still in their infancy, they have shown to further extend the D*o*M reaction when the need for functional group tolerance is paramount and to provide direct functionalization whilst avoiding the need for protecting groups or additional FGIs.

1.6 The D*o*M-Cross Coupling Nexus

The last 30 years have borne witness to an explosion in transition metal-catalyzed methodologies that have heavily impacted the way aryl-aryl bonds are formed.[52] There now exists a plethora of methodologies to form biaryls and heterobiaryls, among which the Suzuki[53] reaction has had the greatest impact due to the stability and low toxicity of boronic acids. The synthesis of the coupling partners is an important part of synthetic

planning; D*o*M offers a convenient one step procedure to functionalized aryl/heteroaryl chlorides, bromides, iodides, triflates, as well as a variety of the alternative organometallic coupling partners for the Kumada-Corriu, Stille, Negishi, Suzuki, and recently Hiyama, reactions for the regioselective Ar-Ar bond formation (Table 1.2).[54]

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



1.43 **1.44** **1.45**

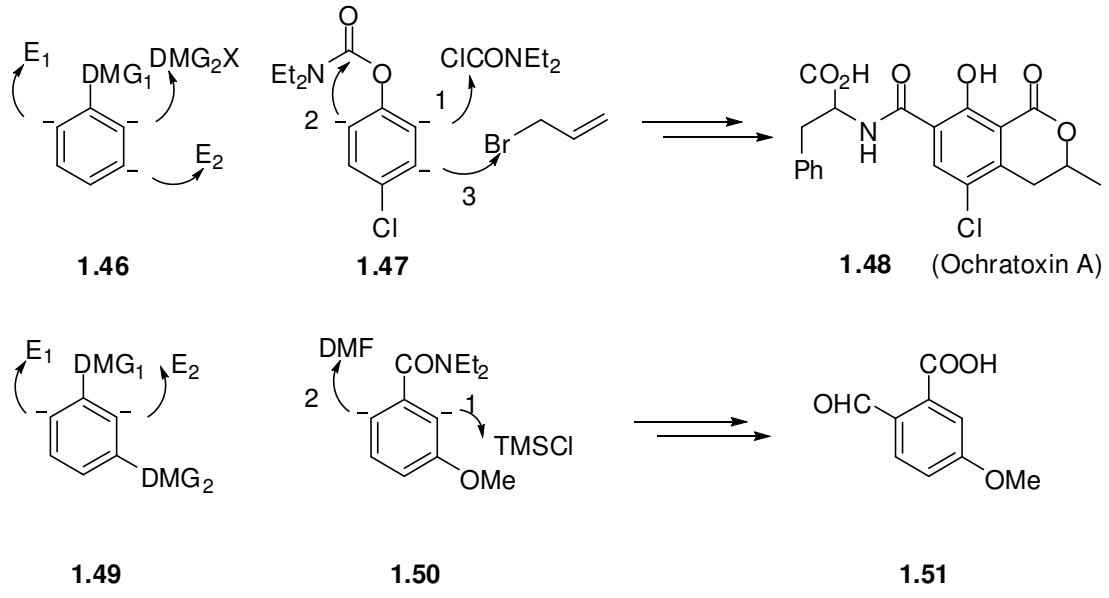
Met	LG	Cat	Xcoupl
$B(OR)_2$	I > Br > OTf	Pd	Suzuki[53a]
MgX	Hal, OTf	Ni	Kumada-Corriu-Tamao[53a]
ZnX	Hal, OTf	Ni	Negishi-Migita[53a]
SnR_3	Hal, OTf	Pd	Stille[53a]
$Si(OR)_3$	Hal, OTf	Pd	Hiyama[53b]
$^1/_3$ In	I, Br, OTf	Pd	Pérez Sestelo-Sarandes[53c]
Zn^{t}Bu$_2$Li	Br	Pd	Kondo[50]
$^1/_3$ MgLi	Br	Pd	Queguiner[46]
Al^{i}Bu$_3$Li	I	Pd	Uchiyam[49]

Not only can biaryl/hetaryl bonds be formed by these processes but a variety of other substitution can be effected via transition metal catalysis such as olefination, alkenylation, and many others.[54] This approach has revolutionized the way that complex structures are constructed; the marriage of D*o*M and cross coupling provides a powerful

methodology that has seen use in medicinal chemistry,[55] material sciences[56] and the total synthesis of natural products.[57]

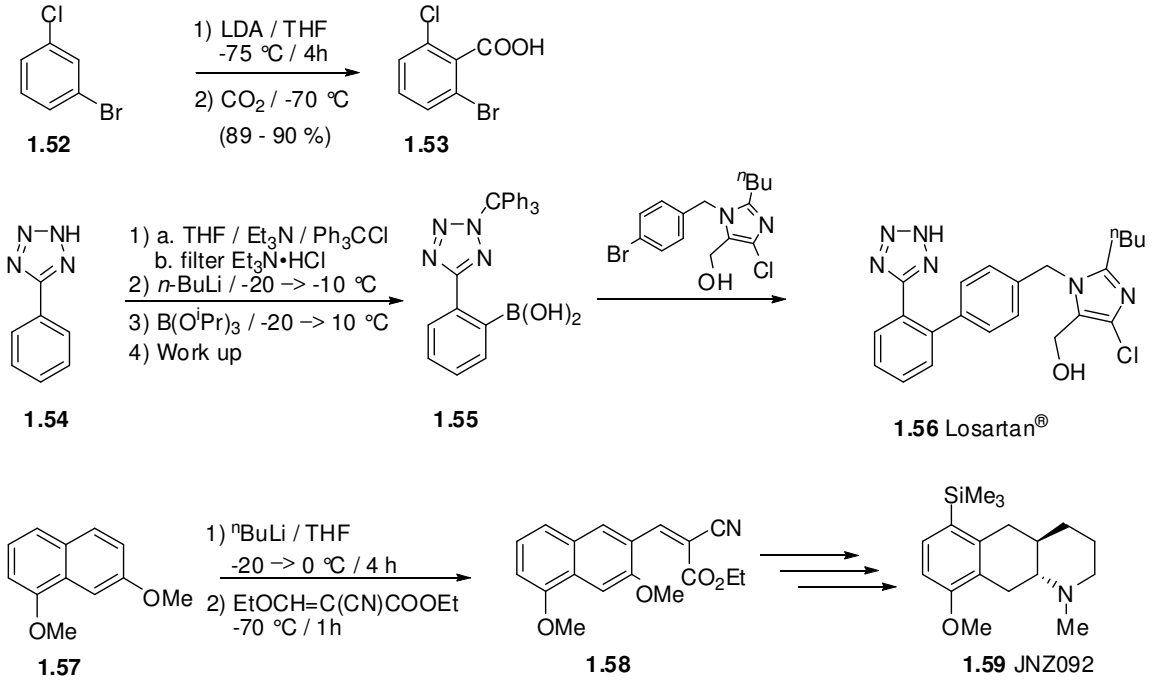
1.7 Applications of the D*o*M Reaction

The high regio- and sometimes chemo-selectivity of D*o*M provides shortcuts to substitution patterns which would otherwise require multiple steps and the use of protection/deprotection sequences. Thus, aryl substitution patterns such as (1,2-, 1,2,3-, 1,2,3,4-, 1,2,3,4,5-) are constructed rapidly e.g **1.46, 1.49**. [58] This is beautifully illustrated in the total synthesis of Ochratoxin A **1.48** (Scheme. 1.9), in which the aromatic core is constructed in three sequential metalations. The use of silyl protection of the more reactive D*o*M site allows for regioselective construction of 1,2,4- uniquely substituted aromatics (**1.50→1.51**). This strategy has been further exploited in the total synthesis of many natural products.[59]



Scheme 1.9 Applications of D*o*M in Synthesis.

The use of D*o*M is not limited to academic pursuits, but also adopted successfully by industry[10] and increasingly applied in large-scale process chemistry for the preparation of advanced drug discovery studies and commercial drugs. The synthesis of 2-bromo-6-chlorobenzoic acid **1.53** in excellent yields (89-90%) on 60 kg scales (Scheme 1.11) has been accomplished by Merck chemists.[10c] In one pot, chemists at BMS were able to use D*o*M to synthesize a tetrazole boronic acid in the first step of the preparation of Losartan™ **1.56**, a drug which is produced 1000 kg/Year.[10e] Metalation of dimethoxynaphthalene **1.57** by Novartis produced the key intermediate **1.58** in 83% for the lead compound JNZ092 **1.59** an anti-depressant, on pilot plant scale.[10d]

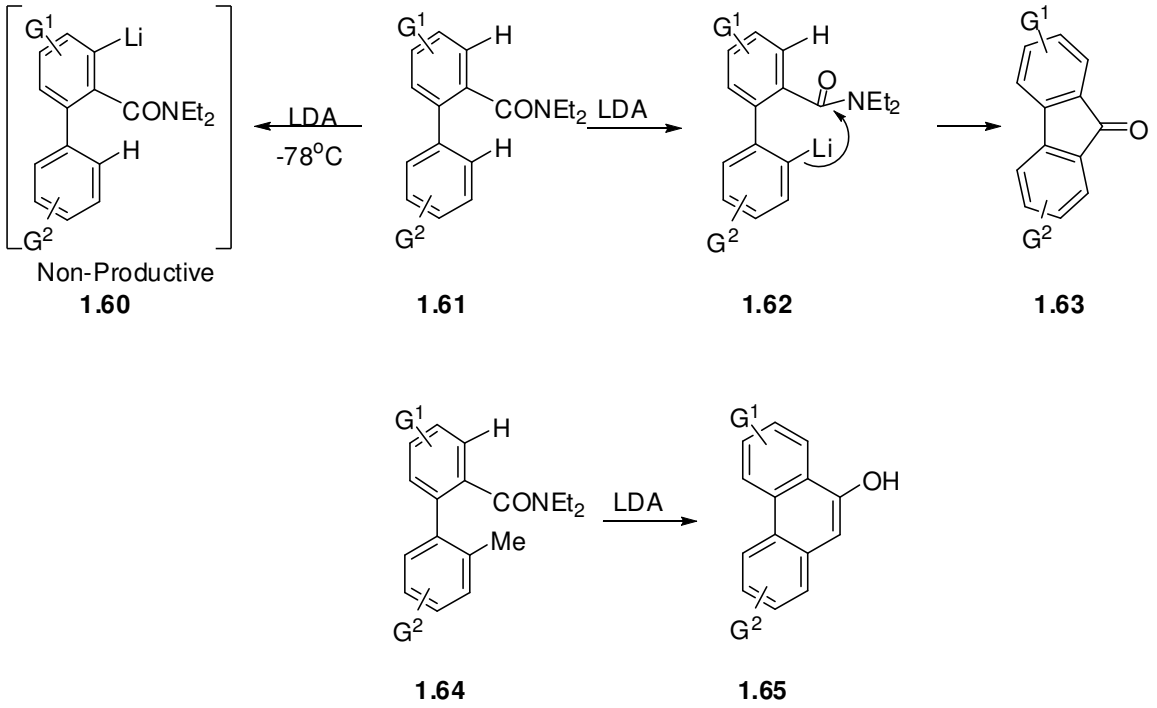


Scheme 1.10 Industrial Applications of D*o*M.

1.8 The Directed *remote* Metalation (D*re*M) Reaction

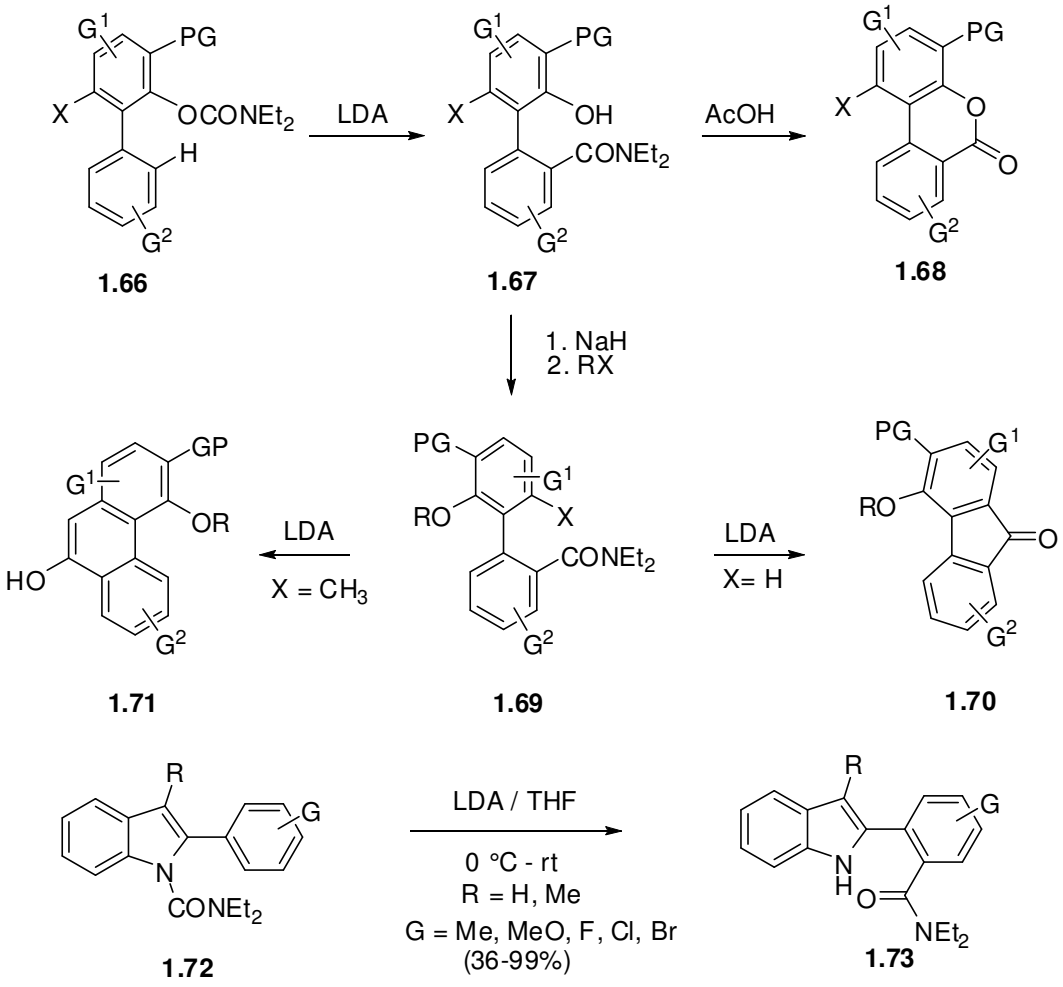
Directed metalation is not limited to *ortho* deprotonation, as discovered in the case of 2-DMG substituted biaryl/hetaryl systems, in which *ortho* metalation is either non-productive or not possible owing to the presence of a 3-subsitutent. In such cases, metalation on other or "*remote"* ring followed by migrations and/or cyclization has been observed. The reaction, dubbed Directed *remote* Metalation (D*re*M), has become a significant synthetic reaction and, although its mechanism has not been extensively studied,[60] it offers support the hypothesis of the CIPE mechanism.

For the DreM reaction involving the tertiary amide **1.60**,[61] *ortho* deprotonation to generate **1.61** occurs under kinetic**,** low temperature conditions, as demonstrated by electrophile quench. If, however an external electrophile is not available, D*o*M is unproductive, and at higher temperatures deprotonation occurs on the remote ring to form **1.62**, which rapidly undergoes cyclization to give the fluorenone **1.63** (Scheme 1.11). Considering the thermodynamic nature of this metalation it is not surprising that also the *ortho* tolyl position **1.64** on the remote ring may be deprotonated under similar conditions, constituting a general route to 9-phenanthrols **1.65** after ring closure**.** [62]



Scheme 1.11 D*re*M Strategies of the Diethylamide.

Biaryl *O*-carbamates **1.66** have proven extremely versatile in the DreM reaction (Scheme 1.12).[63] In the absence of 3-subsitution, the anionic *ortho* Fries rearrangement ensues; however, with base-unreactive or silicon protective substitution (PG), treatment with LDA results in the *remote* migration of the carbamoyl group to give the hydroxy biarylamide **1.67**, a useful intermediate which, for example may can be cyclized to the corresponding dibenzo[x,y]pyranone **1.68**. Alternatively alkylation of the phenol and subsequent treatment with LDA yields the corresponding fluorenone **1.70** or 9-phenanthrol **1.71**. Recently, the reaction of *N*-carbamoyl-2-aryl (and -2-heteroaryl) indoles **1.72** to **1.73** has been demonstrated using LDA.[64]

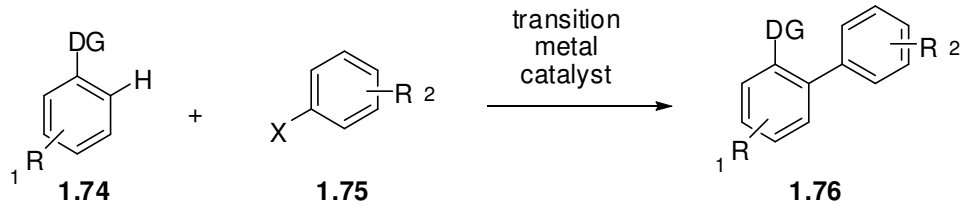


Scheme 1.12 D*re*M Strategies of the Diethylcarbamate.

The D*re*M reaction has been applied to the total synthesis of many natural products,[65] and expanded to provide routes to substituted xanthones,[66] thioxanthones,[67] acridones[68] and dibenzophosphorinones.[69] The application of this strategy to phosphorus based DMGs will be discussed in Chapter 3.

1.9 Transition Metal Catalyzed Directed *ortho*-Arylation / Ir Catalyzed Borylation

Transition metal catalyzed directed *ortho*-arylation has emerged to become an attractive alternative to D*o*M due to the high functional group tolerance and the requirement for only catalytic amounts of transition metals. Although a number of different *ortho*-arylation reactions have been reported, they differ drastically in terms of catalyst, conditions, substrates, and to date no unified mechanism exists. The vast majority of reactions involve the coupling of π-electron-rich substrate possessing a Lewis-basic directing group (DG) with an aryl halide or pseudohalide, (Scheme 1.13).[6] DGs have included but are not limited to pyridines,[6,70] quinolines, [6] pyrazoles,[6] triazoles,[6] imidazolines,[71] oxazolines,[72] benzoxazoles,[73] anilides,[74] benzoic acids,[75] benzaldehydes,[76] and phenols.[77]

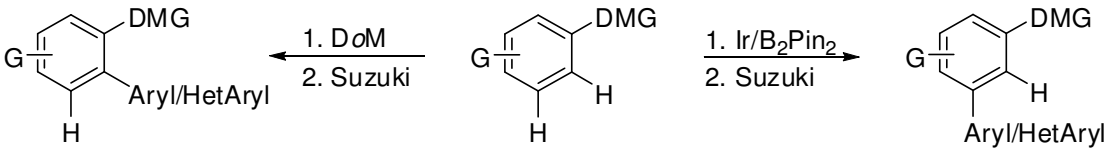


Scheme 1.13 Generalization of the Directed *ortho*-Arylation Reaction.

This rapidly evolving new methodology is both an alternative and complement to the more established D*o*M-cross coupling methodology strategy which appears to have the advantages of avoiding necessity for conversion of functional groups such as carboxylic acids to oxazolines,[78] aldehydes to α-aminoalkoxides,[79] and phenols to OMOM.[80] Directed arylation appears to be sensitive to sterics, and typically proceeds at

the least sterically hindered positions; hence, this methodology may complement D*o*M when 1,3-DG/DMG systems are employed. Directed arylation suffers from the poor ability to control diarylation, especially prevalent when unsubstituted and *para* substituted systems are employed. Further recent development has led to directed coupling of boronic acids[81], and aryltrialkoxysilanes. [82]

The recent discoveries by Smith,[83] and Hartwig and Miyaura,[84] have demonstrated a direct, Ir(I)-catalyzed C-H – activation - borylation of aromatic substrates to yield arylbononates using bis(pinacolato)diboron (B_2pin_2) or HBpin agents (Scheme 1.14). The reaction is highly tolerant of functional groups and regioselectivity appears mainly controlled by steric rather than electronic substituent effects.[85] The resulting boryl species can then be cross coupled, or converted through a variety of FGIs into useful aromatic derivatives. Current work in our group[86] has shown that this reaction may be a powerful method when combined with D*o*M, for the synthesis of functionalization of aromatic substrates.



1.77 **1.78** **1.79**

Scheme 1.14 Comparison of D*o*M and Ir Cat. B_2pin_2 Strategies.

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Chapter 2

Literature Review

2.1 Discovery of Mesoporous Silica

The tremendous impact of zeolites on the chemical industry spurred research in the 1990s to create ordered silica based materials with pores sizes that could accommodate larger molecules. The M41S family of materials produced in the seminal works of Kato[1] and the Mobile Corporation[2] is credited for bringing mesoporous silica to the world stage. The rapid development in this area over the last two decades has been extensively reviewed[3] and has allowed for the precise control of surface area, pore size, mesostructure, and morphology in these unique materials.[4] Due to their high surface area, well defined and ordered pores, these materials have found applications in fields such as sensing,[5] optics,[6] catalysis,[7] adsorption,[8] separation,[9] and host guest chemistry.[10]

2.2 Preparation of Mesoporous Silica

Mesoporous silica can be described as a periodic arrangement of pores within an amorphous silicon oxide framework, whereas zeolites are perfect aluminosilicate crystals. As a result, mesoporous silica does not posses the extraordinary hydrothermal stability of zeolites. However large number of free silanols caused by 3 coordinate defect sites allows for post synthesis functionalization by means of grafting. In addition, mesoporous silica can be prepared in a variety of forms including powders, films,[11] monoliths,[12] and fibers.[13]

The majority of mesoporous silica materials are prepared via the surfactant templating approach. The process can be described as the co-operative self-assembly between the condensing silicate and surfactant: (Figure 2.1) micellar formations associate with the condensing silicate leading to phase separation and liquid crystal formation. This is followed by further polymerization and condensation to strengthen the inorganic silica network.[14] The sieve is typically separated from solution and the surfactant removed by various methods. The charge density of the silicate species initially determines the packing density of the surfactant-silica mix, which in turn dictates the geometry of the surfactant. This is a dynamic process that continues as the material condenses further and reaches a structure of minimal energy.[14] A preformed liquid crystal template can be formed with the surfactant prior to the introduction of the silicate, which requires a significantly larger initial concentration of surfactant and results in a material that is typically more highly condensed.[15]

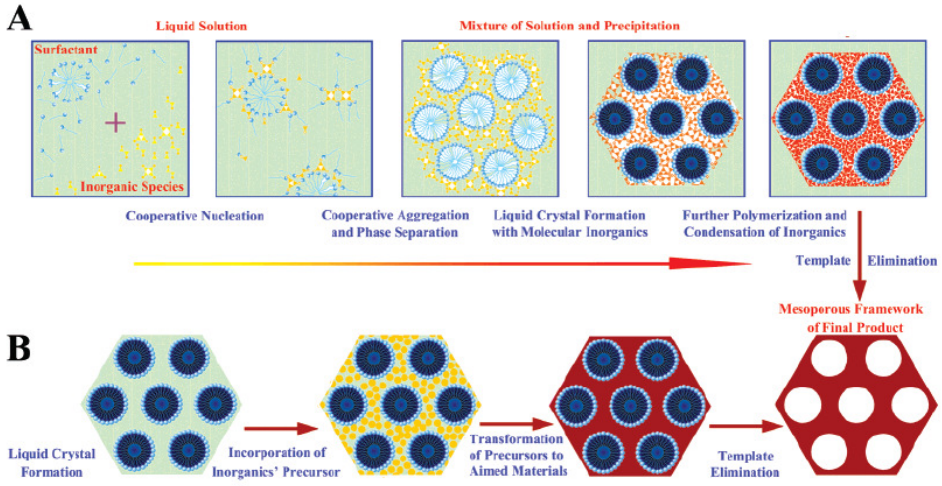

Figure 2.1 The Surfactant Templating Method. Reproduced from Ref 3d.

A surfactant can be classified by the formal charge on its head group. A non-ionic surfactant has no charge while a negative charged specifies an anionic surfactant and a positive charge a cationic species. All three have been used as templating agents to produce mesoporous silica (Figure. 2.2). Cationic surfactants such as CTAB (cetyl trimethylammonium bromide) have been extensively employed under both acidic and basic conditions and have been shown to produce a variety of mesostructures.[16] Anionic surfactants[17] are less prevalent and non-ionic surfactants such as polyethers P-123 and F-127 (Figure 2.2) have been used extensively to generate high quality materials.[18]

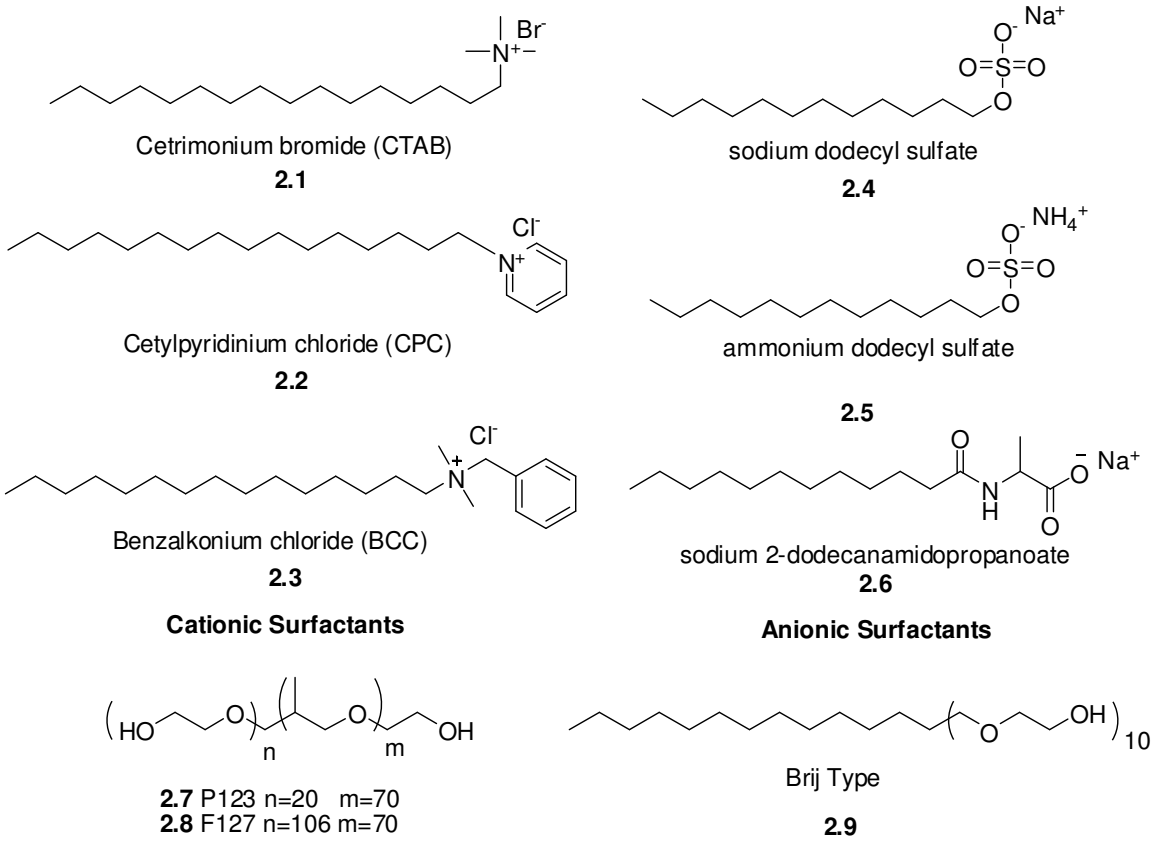

Figure 2.2 Common Surfactants.

The interaction between the surfactant and the condensing silica matrix plays an important role in the resulting material. There are considered to be six modes of interactions depending on the type of surfactant used, counter ions present, and the pH at which the material condenses (Figure. 2.3).[19] Graphic **A** illustrates the ionic interactions between both anionic and cationic surfactants detonated (S^-, S^+) and the condensing inorganic silicate species are denoted (I^- ,I^+). The nature of the inorganic silicate species can be typically controlled by pH, acidic conditions favouring I^+, and basic I^- species.[19] Graphic **B** displays an ion pairing between the surfactant, counterion, and condensing silicate. The counter ion has shown to be important affecting the structure, morphology and stability of the material. [20] Non-ionic surfactant interactions are shown in **C** as a S^0I^0 interaction under neutral conditions or $S^0(X^-I^+)^0$ under acidic conditions.[21]

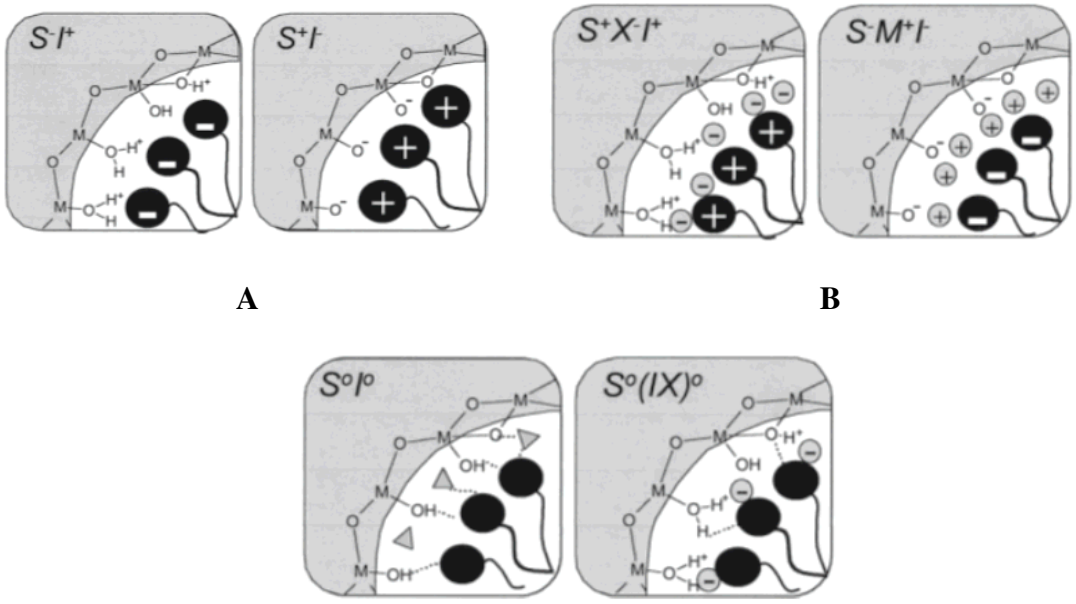

Figure 2.3 Surfactant Silicate Interactions. Reproduced from Ref. 19

MCM-41 is one of the most widely used materials due to its high surface area, large pores, and a two-dimensional hexagonally ordered mesostructure. It is formed using the surfactant (CTAB) cetyl-trimethylammonium bromide under basic conditions[3C] pore size can be controlled by shortening or lengthening the alkyl chains of the surfactant or by the addition of a pore swelling agent such as 1,3,5-trimethylbenzne. The mesostructure of MCM-41 can be altered from 2-D hexagonal (**A)** to the less stable cubic arrangement (**B**) by increasing the surfactant:silica ratio or by adding co-solvents such as EtOH and BuOH which change the solvent packing parameter (Figure 2.4).[22]

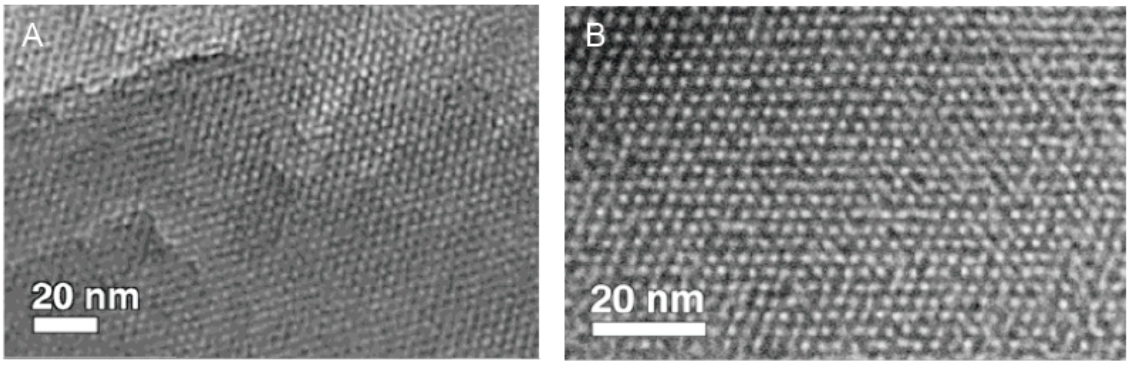

Figure 2.4 A) MCM-41, B) MCM-48. Reproduced from Ref.22

In 1998 another breakthrough came from Stucky and co-workers at University of California, Santa Barbara who produced SBA-15,[18] a mesoporous silica templated with the non-ionic surfactant P123 which has proven to be one of the most stable, and easily prepared mesoporous silicas. Similar to MCM-41, SBA-15 is 2D hexagonally ordered, but has larger pores and thicker walls imparting greater hydrothermal stability. Control of the pore size can be accomplished by altering the time and temperature of post condensation hydrothermal treatment or by using a pore swelling agent such as TMB to

achieve pore sizes of 300 Å. A feature of SBA-15 and other materials prepared using non-ionic block co-polymers as surfactants is that they have microporous walls that actually interconnect and display long range order, a property that is thought to occur by intercalation of ethylene oxide blocks during condensation. Evidence for this can be seen by platinum casting of SBA-15 which maintains hexagonal order after removal of silica.[23]

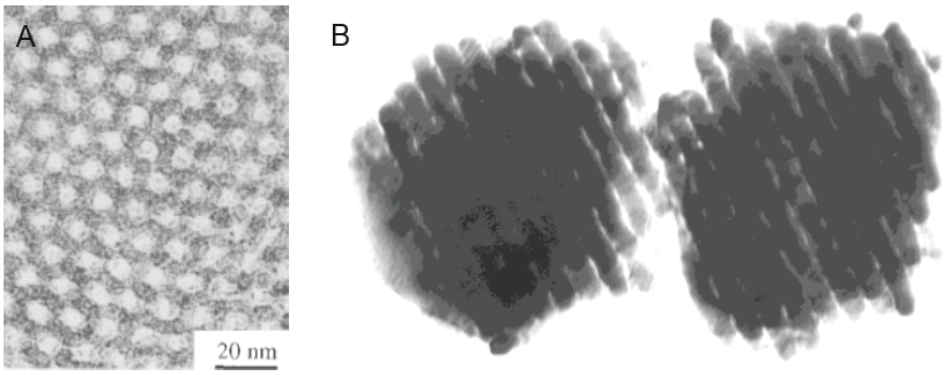

Figure 2.5 A) SBA-15, B) Pt Castings. Reproduced from Ref. 22

Changing the ratio of hydrophilic/hydrophobic blocks within these surfactants can have an effect on the mesostructure. SBA-15 uses P123 (Figure 2.2) and produces a 2D hexagonal packing, while the use of F123, in which there is an increase in the hydrophilic blocks, yields SBA-16 which has cubic order.[18]

Removal of the surfactant is typically accomplished via calcination, i.e., heating the silicate to high temperature resulting in oxidative decomposition of the surfactant. This method is advantageous due to its simplicity, speed, and scalability. To maintain order in the material, the rate of heating must be controlled to 1-2^{o}C/min, with the final

temperature being maintained for 4-6 h. Higher temperatures results in decreased surface area and pore size/volume, in addition there is a significant reduction in the presence surface silanols, which limits the extent that post-condensation functionalization through grafting.[24] Calcination is only suitable for materials composed of pure silica; materials functionalized with organic species cannot be calcined without danger of removing the organic groups as well. Extractive removal of the surfactant is a milder alternative, which results in smaller pore size contraction and leaves larger numbers of hydroxyl groups on the surface. [25] Extraction is typically performed using ethanol or THF, often in the presence of dilute acid to improve the degree of cross linking of the silica, which is generally lower under acidic conditions. [25] However complete removal of the surfactant can be sometimes be a concern. Other methods for surfactant removal that have been employed are UV irradiation,[26] microwave irradiation,[27] and super critical carbon dioxide extraction.[28]

2.3 Characterization Methods

Unlike small molecules, solid state mesoporous materials cannot be adequately characterized by traditional methods. Methods employed are SEM, TEM, pXRD, MAS NMR, and nitrogen/argon porosimetry. Scanning electron microscopy (SEM) is used to examine the outside of the material and gives information about the morphology. SEM relies on the conductivity of the material. Although many times the material can be observed directly, coating the surface with a conductive metal such as gold often provides higher resolution. Powdered materials can produce various morphologies such as

spheres[29], rods[30], and even helixes.[31] Alternatively, transmission electron microscopy (TEM) provides higher resolution of the material, often to the nm scale, and is used to characterize pore structure and short range order, whilst powdered x-ray diffraction is used to examine long range order and pore size on a bulk sample.

Solid state NMR can be used to probe active nuclei present in the material. Most commonly ^{29}Si NMR has proved to be quite a powerful method, providing the speciation of silica and their relative ratio in the material. Resonances observed from -90 to -120 ppm are attributed to Q_n sites, n denoting the number of Si-O-Si bonds present, and gives an indication of degree of condensation in purely siliceous materials.[18] Analogously, for organically functionalized silica[32] T_n resonances (-60 to -85 ppm) refer to a carbon directly bound to silicon, where n represents the number of Si-O-Si bonds present. Additionally, other nuclei can be observed such as ^{13}C, ^{11}B, and ^{31}P, which are particularly useful when examining organically functionalized materials.

Gas porosimetry is among the most important and widely used method for the characterization of mesoporous materials, due to the quantitative information that it provides about surface area, polarity and pore structure.[33] Nitrogen gas is commonly employed for the characterization of mesoporous materials due to its low cost and ease of availability although argon can be employed as well. Isotherms commonly observed with ordered type silica can be classified by IUPAC type 1 and type IV as shown in Figure. 2.6.[34]

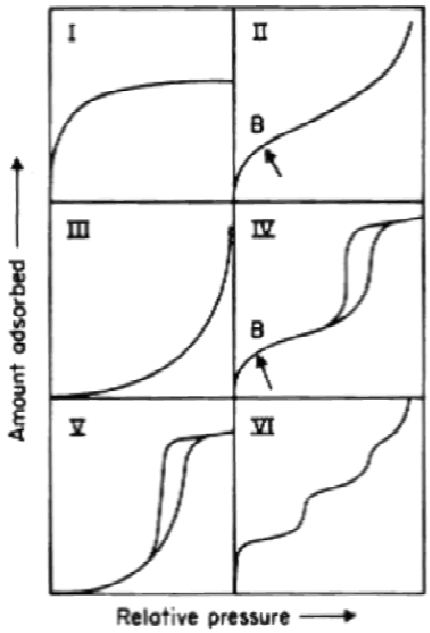

Figure 2.6 IUPAC Isotherms. Reproduced from Ref 32.

Type I isotherms can be characterized by significant adsorption at low relative pressures, indicative of a microporous material, or of mesoporous materials having small pores and/or broad size distributions. Type IV isotherms display a gradual steady adsorption at low relative pressures which is followed by a large adsorption at intermediate relative pressures. This abrupt adsorption is due to a condensation into the pores a phenomenon known as capillary condensation.[35] Similarly, upon desorption, capillary evaporation occurs, however the desorption of gas from the pores does not occur at the same relative pressure that it enters, resulting in a hysteresis loop. The difference is attributed to both the thermodynamic metastability of the gas phases both in and out of the pore. [36] Current models based on the Kelvin-Cohan Equation equation (Eq.1) can explain the appearance of the hysteresis loop.[35c] For open cylindrical pores the

term r_m denotes the radius of curvature of the meniscus, r_m can derived from where r_1 and r_2 denoting the radius and height of the pore respectively (Eq.2). Upon condensation $r_2 = \infty$ because the pore is open, whereas upon evaporation $r_m = r_1 = r_2$ because the pore is closed.

$$\ln\left(\frac{P^*}{P_0}\right) = -\left(\frac{2\gamma v \cos\theta}{RTr_m}\right) \qquad \frac{1}{r_m} = \frac{1}{2}\left(\frac{1}{r_1} + \frac{1}{r_2}\right)$$

Eq. 1. **Eq. 2.**

From the model, the relative pressure for condensation and evaporation must be different, forming the hysteresis. This model accounts for this phenomenon but does not necessarily explain it. It is important to take into account that the pores are not individually entities but are interconnected as evidenced by Pt castings.[23] Pore interconnectivity has been proposed to account for the hysteresis effect, the pores fill in the usual manner however evaporation occurs by spontaneous cavitation at the critical P/Po limit.[37] Another model proposed attributes the hysteresis to elastic deformation of the pores, constriction and expansion of the pores changing the meniscus.[38] Significantly, surface and pore properties can be calculated from these results using various methods. The Brunauer-Emmett-Teller (BET) method[39] can be used to estimate the surface area, whilst pore volume, pore size, and distribution are commonly estimated by Barrett-Joyner-Halenda (BJH) method for materials with pores greater than 20 Å.[40]

2.4 Functionalization of mesoporous silica

Unlike zeolites, completely siliceous materials lack the reactive centers to facilitate in many chemical processes and thus have limited applications. However, the presence of surface silanols allow for the further introduction of various organo siloxylanes and silyl chlorides (Figure 2.7), providing an excellent support for many organic functionalities. Grafted materials have found utility in numerous applications and have been reviewed extensively.[41]

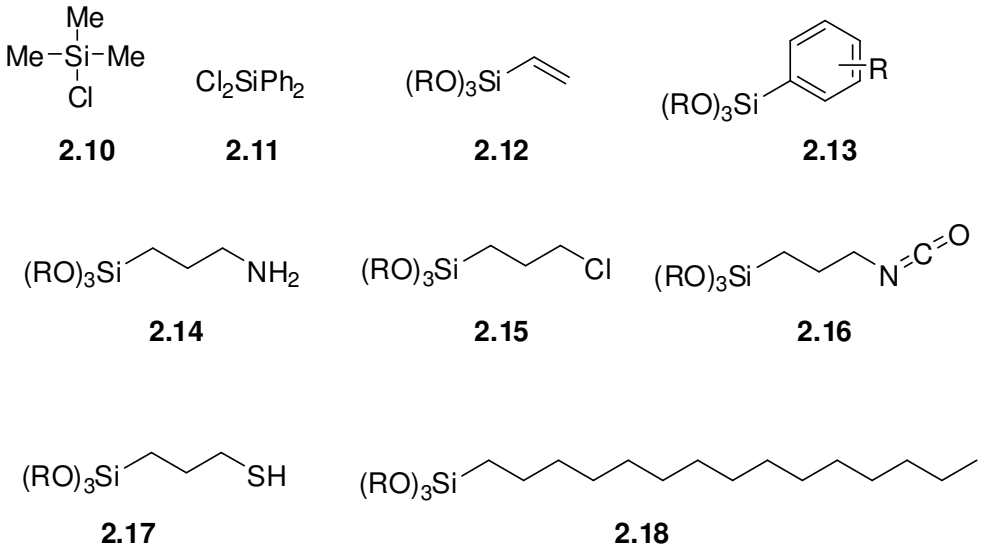

Figure 2.7 Common Grafting Agents.

The possibility to functionalize a regularly ordered material with a high surface areas is an attractive one; however, while grafting is a common technique, it can be limited often by poor loading and batch to batch irreproducibility. Upon closer examination, MCM-41 was found to form hydrophobic and hydrophilic domains upon

calcination, the hydrophobic zones becoming preferentially grafted.[42] Feng and co-workers showed that carefully controlling the exact amount of water adsorbed on the surface could allow up to 76% surface coverage with MPTMS **2.17**.[43] The surface properties of materials can also be modified by using silyl chlorides, such a TMSCl **2.10** to effectively cap free silanols and increase the hydrophobilicity of the surface.[41b]

Post condensation grafting is not the only option to functionalize materials. Co-condensation of the silicate with organo siloxylanes has been shown to be a viable option giving a more homogenous distribution of the organic functionality with less dimunition in pore size, however, the accessibility of that functionality may be limited due to condensation inside the pore walls.[44] Co condensed methods allows for the preparation of materials that posses organic functionality in addition to surface silanols for further grafting.

Progress towards selective functionalization of either the surface or the pores has been slow.[45] Current work performed by Jonathon Webb in the Crudden group has focused on the synthesis of materials which possess catalytic functionality exclusively within the pores, and therefore would provide materials which eliminate contributions from catalysis on the external surface.[46] The method relies on treating the as-synthesized material that has surfactant remaining in the pores with a passivation agent such a TMS-OMe which caps the exposed silanols, followed by extraction and functionalization of the mesopores with MPTMS (Figure 2.8).

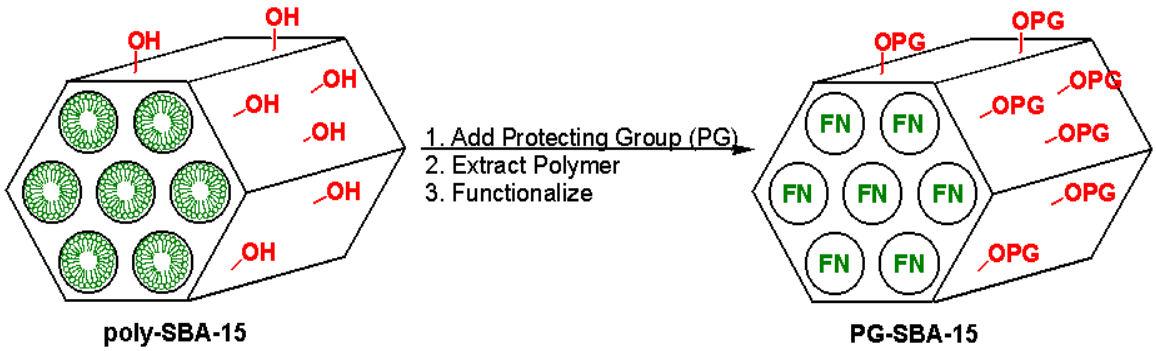

Figure 2.8 Pore Protection Method. Figure courtesy of Jonathan Webb.

2.5 Applications of mesoporous silica

Mesoporous silica materials functionalized with organic monolayers of mercatopropylsilane have been found to be extremely efficient in removing mercury and other heavy metals from both aqueous and nonaqueous waste, with distribution coefficients up to 340 000.[43] The materials were found to be fairly stable and even reusable, with applications for heavy metal remediation, waste stabilization, water treatment, and metal recovery.

The Crudden group has immobilized a Cinchona alkaloid derivative on SBA-15 (Figure. 2.9, **2.19**) to provide a solid supported chiral ligand for use in asymmetric dihydroxylation.[47] The chiral ligand grafted onto mesoporous silica was catalytically active for the dihydroxylation of disubstituted olefins with enantioselectivities of >90 % ee matching those that were obtained in solution, and exceeding those obtained with the same ligand immobilized on amorphous silica.

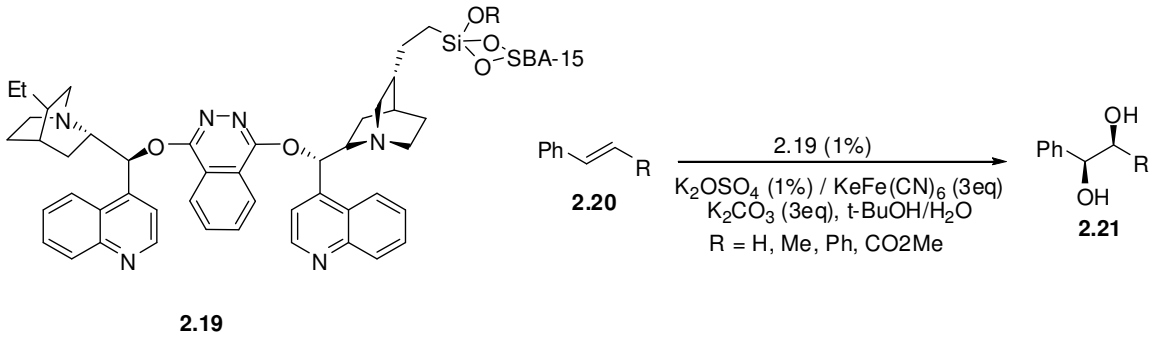

Figure 2.9 The Cinchona Alkaloid Derivative on SBA 15.

Functionalized materials have also been utilized as supports for metals used in transition metal catalysis. A number of functional groups have been grafted onto mesoporous silica materials to immobilize palladium to perform cross coupling reactions.[48]

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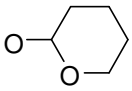
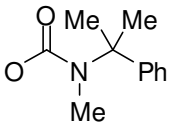
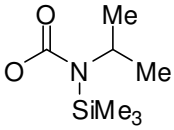
Chapter 3

The Development of the *N,N,N',N'*-Tetraethylphosphorodiamidate DMG

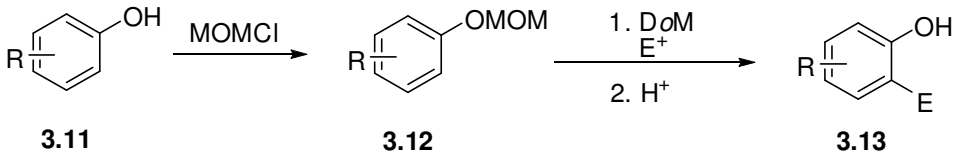
3.1. Developing new Phenolic Based DMGs

Phenolic based DMGs are among the most common heteroatom based DMGs, which include the readily prepared OMe **3.1**,[1] OMOM **3.2**, [2] OTHP **3.3**, [3] and OSEM **3.4**[4] (Table 3.1). Although exhibiting modest directing power, they are highly resistant to nucleophilic attack allowing metalation to be performed at room temperature.

Table 3.1 Common Phenolic DMGs.

OCH_3	**3.1** (Gilman-Wittig, 1938)[1]	$OPO(OEt)_2$	**3.7** (Melvin, 1981)[8]
OCH_2OCH_3	**3.2** (Christensen, 1975)[2]	$OPO(NMe_2)_2$	**3.8** (Näsman, 1986)[9]
	**3.3** (Cassidy, 1957)[3]		**3.9** (Snieckus, 1999)[10]
$OCH_2OCH_2SiMe_3$	**3.4** (Snieckus, 1990)[4]		
$OCONEt_2$	**3.5** (Snieckus, 1983)[6]		**3.10** (Hoppe, 2001)[11]
OSO_2NEt_2	**3.6** (Snieckus, 2005)[7]		

Several of the groups, such as OMOM, may be cleaved under mild acidic conditions allowing their selective removal post D*o*M chemistry. This strategy is practiced routinely in the synthesis of *ortho* substituted phenols (Scheme 3.1). [5]



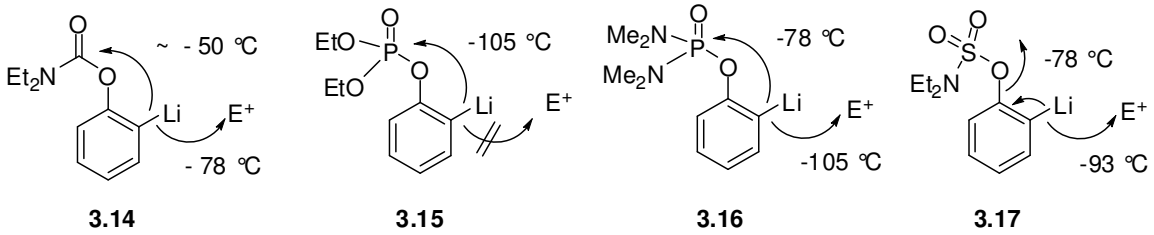
3.11 **3.12** **3.13**

Scheme 3.1 D*o*M Strategy for *ortho* Phenols.

In comparison, DMGs such as the diethyl *O*-carbamate **3.8**,[6] diethyl *O*-sulfamate **3.7**,[7] diethyl *O*-phosphonate,[8] and N,N,N',N'-tetramethyl-*O*-phosphoramidate[9] are stronger coordinating groups. They, however, are sufficiently resistant to hydrolytic cleavage and reductive methods, requiring harsher less selective methods for conversion to the corresponding phenols. The *N*-cumyl **3.9**[10] and the *N*-TMS *O*-carbamate group **3.10**[11] (Table. 3.1) were rationally designed to circumvent this problem, combining the strong directing power with mild deprotection.

Although strong directing DMGs have the advantage of providing efficient *ortho* deprotonation (as ascertained by D_2O or MeOD quench experiments) many phenolic based DMGs are susceptible to nucleophilic attack and anionic rearrangements. The anionic *ortho* Fries rearrangement which is formally a 1,3 *O-C* migration of the electrophilic center of the DMG to the *ortho* lithiated aryl species (Scheme 3.2) is a synthetically very useful feature. This is a function of the DMG, temperature, steric effects, and base. The *O*-diethylcarbamate **3.14** can be effectively lithiated at -78^{o}C and trapped with a suitable electrophile to build 1,2- disubstitution, however left to warm to approximately -50 ^{o}C, the *ortho*-lithiated species undergoes the anionic Fries leading to the corresponding salicylamide which is a useful intermediate. Perhaps more

significantly, after phenol protection, can be used for further amide DMG metalation chemistry.[12] The diethylphosphonate **3.15** which is even more reactive, cannot be trapped with an external electrophile since it undergoes the phospha-Fries or *P-ortho*-Fries rearrangement at -105 ^{o}C, thus restricting the synthetic application of the DMG.[8,13] Watanabe showed that the more hindered *ortho* lithiated phosphorodiamidate **3.16** is stable at -105^{o}C but undergoes P-*ortho*-Fries rearrangement at higher temperatures (-78 ^{o}C).[14] Metalation- electrophile trapping of an aryl *O*-sulfamate **3.17** is carried out at –93 °C, since at -78 ^{o}C the DMG is eliminated with formation of a benzyne as confirmed by furan trapping experiment.[7]



3.14 **3.15** **3.16** **3.17**

Scheme 3.2 Stability of Phenolic DMGs.

3.2. The Importance of Organophosphorus Compounds

The synthesis of new organophosphorus compounds is a worthwhile endeavor, and although organophosphorus compounds receive relatively little attention they enjoy extensive and often significant industrial use (Figure. 3.1). Perhaps the most well known organophosphorus compound among organic chemists is triphenylphosphine (**3.18**), a common chemical reagent.[15] Zinc dialkyldithiophosphates (**3.23**) are manufactured on

kiloton scales for use in lubricants as antioxidants. SPhos (**3.19**) developed by Buchwald[16] is one of the most active phosphine ligands in the now very common palladium catalyzed Suzuki-Miyuara reaction. Organophosphorus compounds are among some of the most biologically active compounds known, for example, VX (**3.24**), is manufactured for use in chemical warfare has an LD_{50} of only 10 mg.[17] Reclast (**3.20**) is an extremely potent bone reabsorption drug used to treat osteoporosis,[18] and cyclophosphamide (**3.21**) is extensively used in chemotherapy.[19] Agrochemicals such glyphosate **3.22** more commonly known as Roundup™, revolutionized the farming industry overnight.[20] This sampling demonstrates the value of organophosphorus compounds have in the industrialized world.

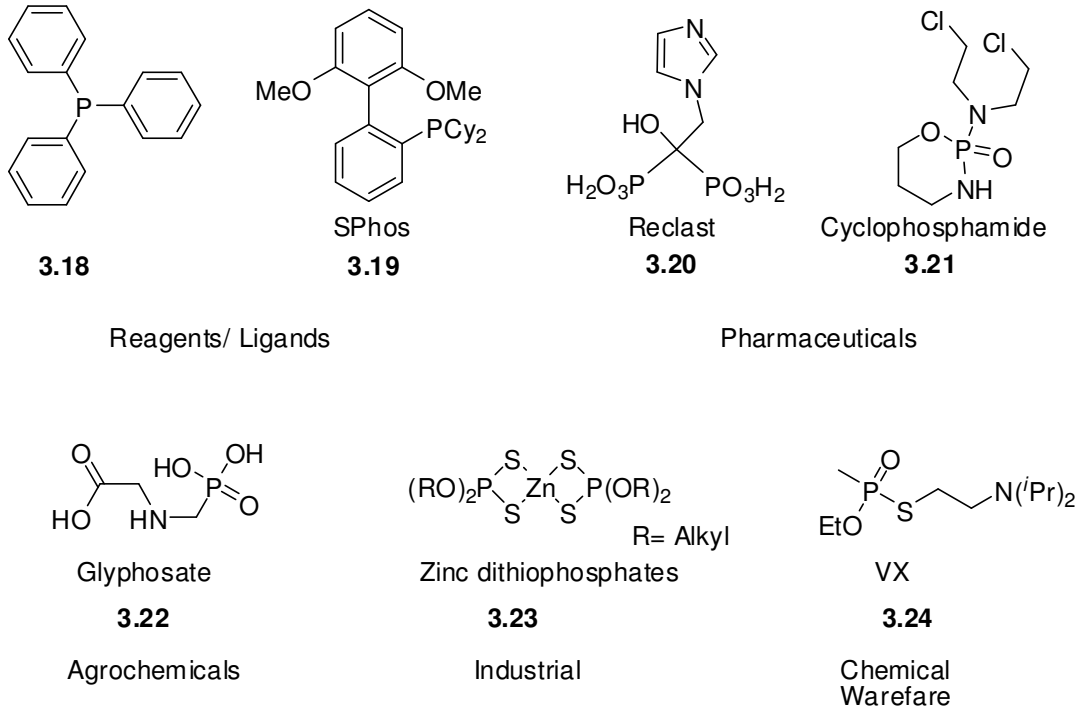
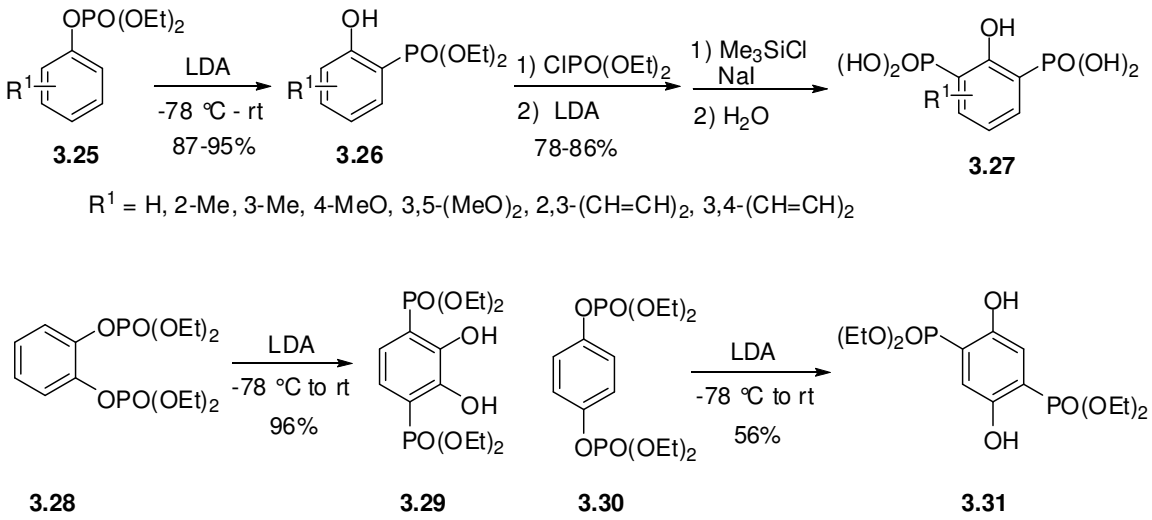


Figure 3.1 Industrially Relevant Organophosphorus Compounds.

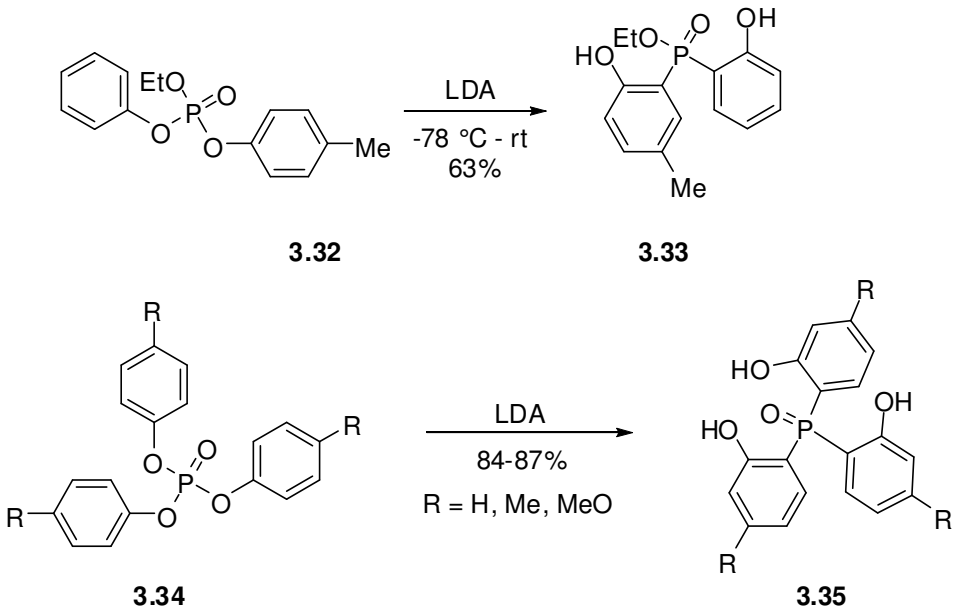
3.3. The Phosphate and Phosphorodiamidate DMGs

The first use of phosphorus-based DMGs was by Melvin,[8] and Cambie,[21] who demonstrated the anionic P-*ortho*-Fries. However, it was Redmore who applied this reaction, developing the methodology to construct unique *o*-hydroxyphenylphosphonic acids (Scheme 3.3). This methodology was further expanded demonstrating migrations of aryl 1,2- and 1,4-diphosphates.[22]



Scheme 3.3 Synthetic Methods for *o*-Hydroxyphenylphosphonic Acids.

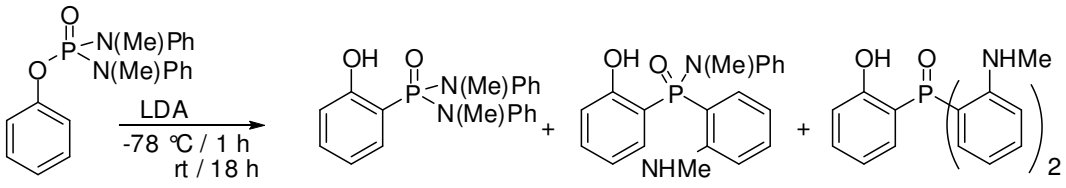
Redmore cleverly applied this method to double phosphyl migrations of diarylphosphate esters to prepare unique diaryl phosphates (Scheme 3.4). This was further expanded to include triple migrations to form *o*-hydroxy triaryl phosphine oxides.[23]



Scheme 3.4 Double and Triple Rearrangements of Phosphate Esters.

Modro studied similar multiple migrations of the phosphorodiamidate **3.36** (Table 3.2).[24] The results show that the rate of *O-C* migration is substantially more favorable than *N-C* migration, most likely due to the leaving group ability of the phenolate vs. anilide species.

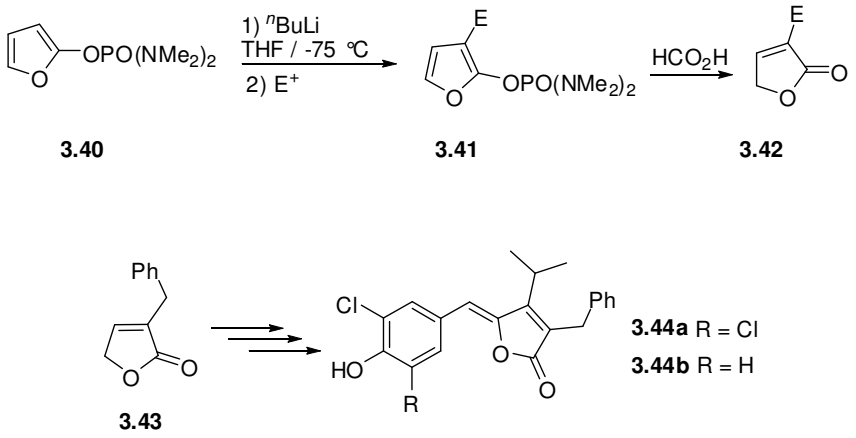
Table 3.2 Product Distribution of *C-O* vs. *C-N* Migration upon Metalation of 3.36.



3.36

LDA (equiv)	**3.37** (Yld %)	**3.38** (Yld %)	**3.39** (Yld %)
1.0	71	---	---
4.0	20	76	4
8.0	16	79	5

Näsman[9] was the first to report the use of the $OPO(NMe_2)_2$ group as a DMG in 1986, showing that *ortho* metalation of **3.40** followed by electrophile quench and hydrolytic cleavage of the phosphorodiamidate group produces a variety of 3-substitued 2-furanones **3.42**, compounds not easily made by classical methods (Scheme 3.5). This approach to substituted furanones was employed to construct **3.43**, an intermediate in the total synthesis of cytotoxic lactones nostoclides I and II (**3.44a,b**)[25] and a series of related derivatives displaying inhibitory activity on the photosynthetic electron transport chain.[26]



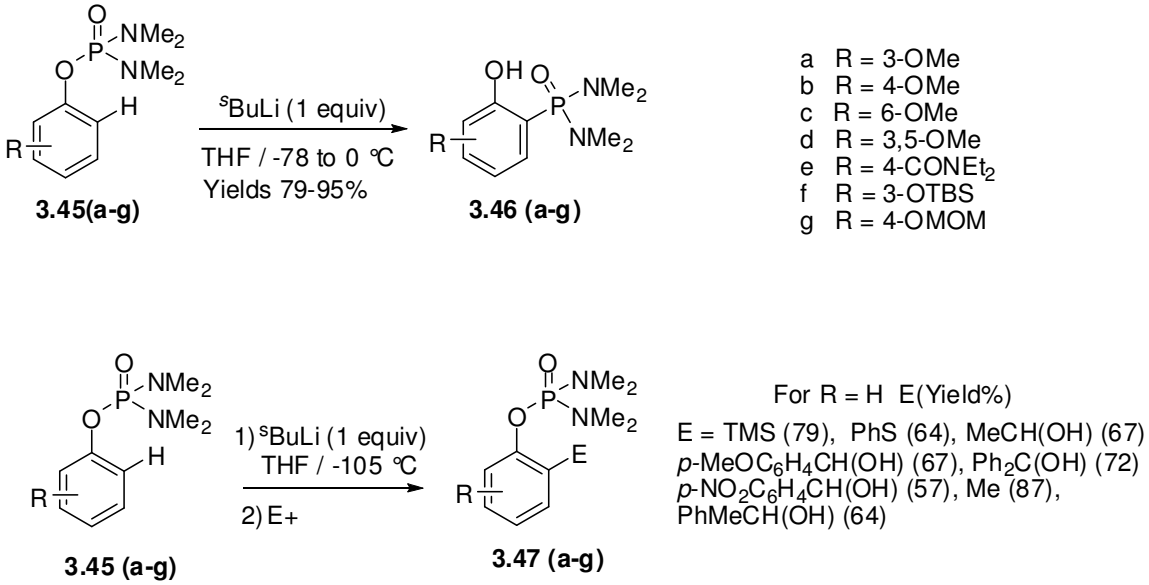
3.41

E^+	Yld (%)
MeI	95
TMSCl	89
DMF	60
BnI	15
BnBr	55
PhSSPh	57
Me_2CO	46
PhCOMe	65
ThienylCHO	57
PhCHO	55
$PhCH_2OCH_2Cl$	50

Scheme 3.5 DoM on 2-Furyl Phosphorodiamidates 3.40.

Watanabe systematically explored the potential of the $OPO(NMe_2)_2$ group as a DMG in the *ortho*-metalation of aromatics **3.45** (Scheme 3.6).[14] The *ortho* lithiated species was found to be unstable at -78 °C, rapidly undergoing rearrangement to the 2'-hydroxyarylphosphonic diamide **3.46**. Suppression of the *P-ortho*-Fries was accomplished by using temperatures of -105 °C, allowing external quench with an extensive number of electrophiles to furnish products **3.47**. Substrates that possessed

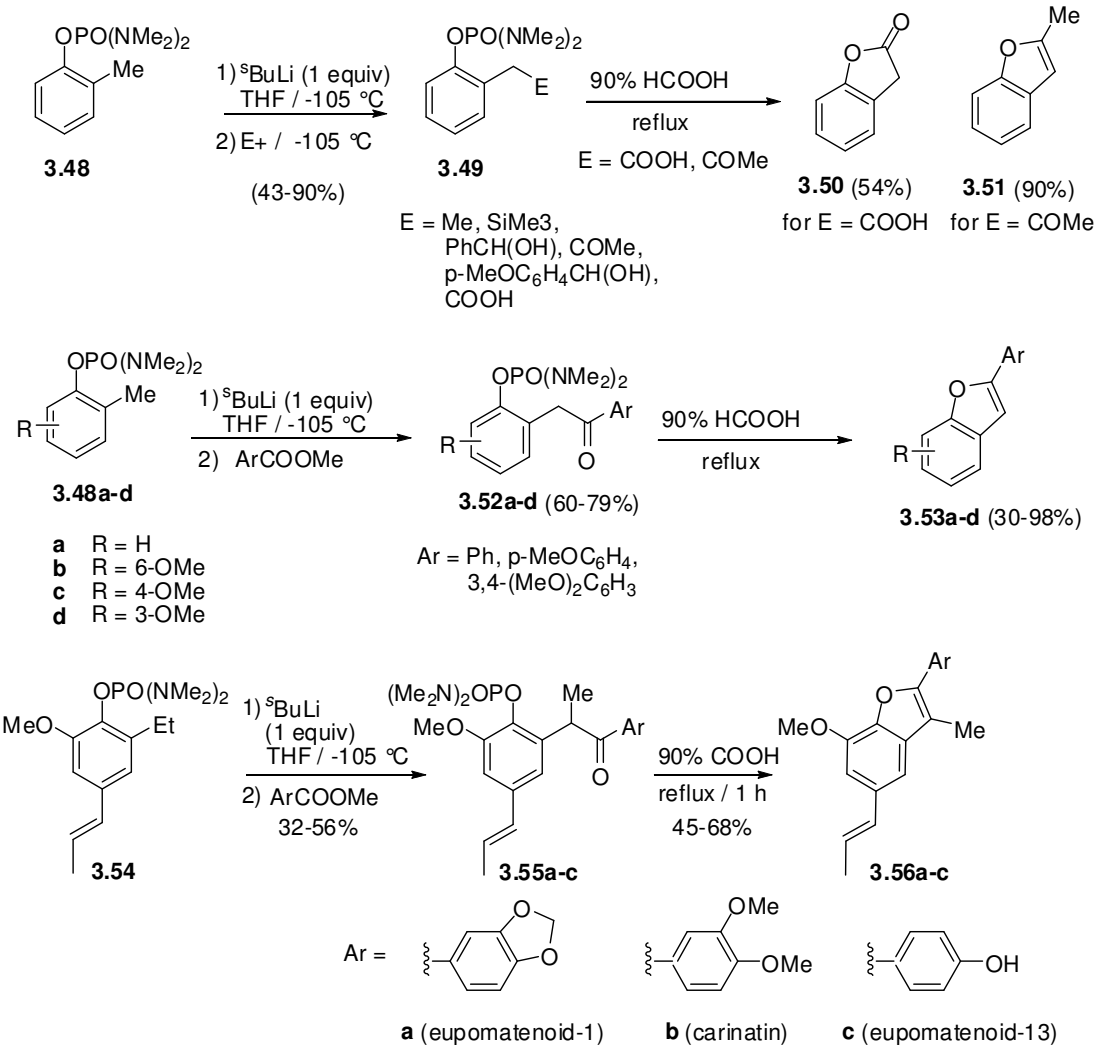
methoxy groups at the *meta* position (**3.45a,d)** showed excellent in-between metalation regioselectivity demonstrating the synergistic effect of the phosphorodiamidate DMG and the weaker methoxy DMG. An intramolecular competition experiment on **3.45e** was found to occur *ortho* to the $OPO(NMe_2)_2$ rather than to the *para*-diethyl *O*-carbamate under kinetic conditions. Inferring a stronger coordinating ability of the former DMG. Finally **3.45f** displayed metalation at C-6, most likely due to steric blocking of the C-2.



Scheme 3.6 Generalization of the D*o*M reaction on Aryl Phosphorodiamidate 3.45.

Watanabe also compared[27] the directing power of the $OPO(NMe_2)_2$ DMG with other DMGs through intermolecular and intramolecular competition studies and found it to one of the most powerful DMGs to date. Thus, it is threefold stronger than the $CONEt_2$ group, fourfold stronger than the $SO_2{}^tBu$ group, and even twice as strong as the powerful $OCONEt_2$ group. Later examining substituted *o*-tolylphosphorodiamidates **3.48**

Watanabe found that the $OPO(NMe_2)_2$ group is a strong lateral director and that benzylic positions readily undergo metalation and substitution **3.49** (Scheme 3.7). [27]

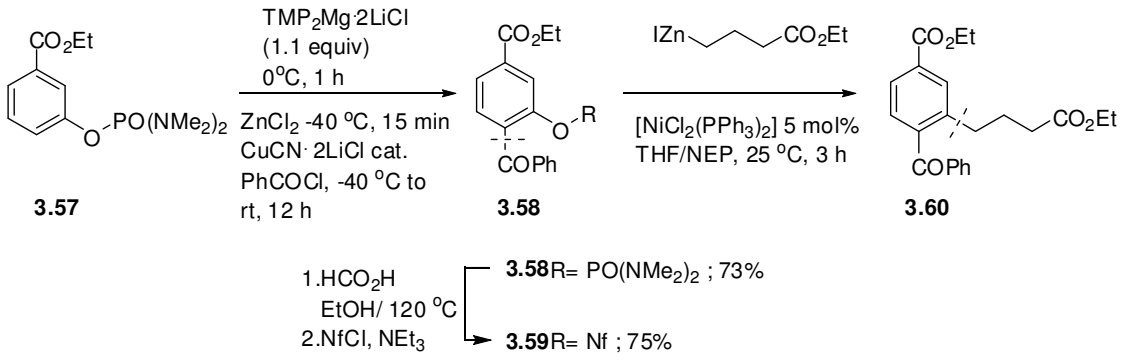


Scheme 3.7 Generalization and Application of Lateral Metalation of *o*-tolylphosphorodiamidates 3.48.

Introduction of carbonyl electrophiles allows the formation of benzofurans **3.51** and benzofuranons **3.50** through one-pot hydrolytic cleavage of the phosphorodiamidates

and subsequent intramolecular cyclization. This type of sequence was generalized to produce substituted 2-aryl benzofurans **3.53a-d** and later incorporated into the total synthesis of three natural products, carinatin **3.56a**, eupomatenoid-1 **3.56b**, and eupomatenoid-13 **3.56c**.

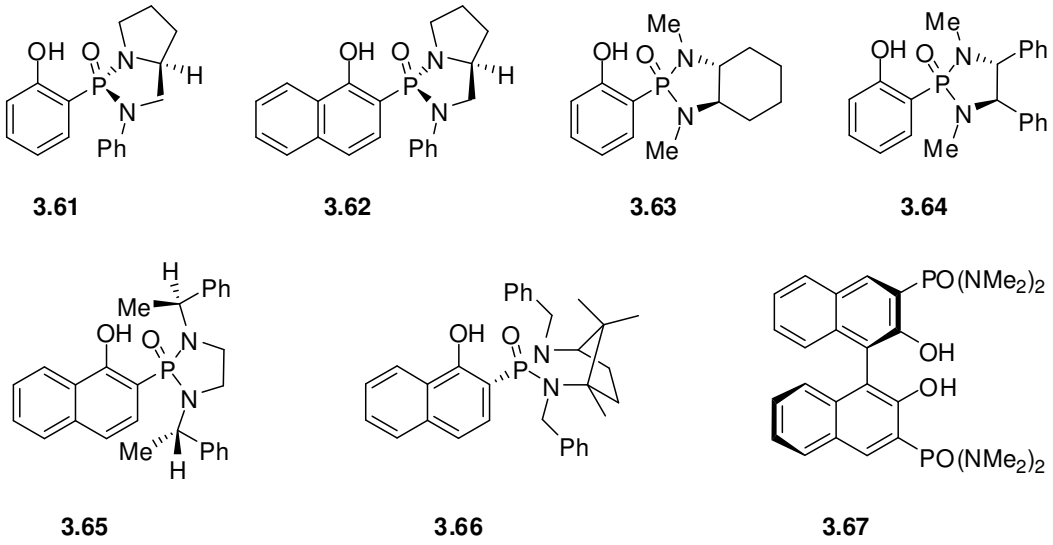
Recently, Knochel demonstrated the use of the mixed Li/Mg base $(TMP)_2Mg{\bullet}LiCl$ in the *ortho* metalation of arylphopshorodiamidates (Scheme 3.8). [28] Not only did this procedure allow *ortho*-magnesiation of aryl and pyridine rings at temperatures of -40 ^oC -to 0 ^oC without complications of the *P-ortho*-Fries, but the reaction could also be carried out in the presence of substituents which are normally incompatible with alkyllithiums such as COOEt, COO^iPr, COO^tBu, and CN. Particular emphasis was dedicated to the synthesis of 1,2,4-trisubstituted arenes as illustrated by the synthesis of **3.60**. Unusually, in the presence of weakly synergistic DMGs *meta* to the $OPO(NMe_2)_2$, metalation preferentially occurred at the least sterically hindered position.



Scheme 3.8 Example of *ortho*- Magnesiation of Phopshorodiamidates.

The hydrolysis of the phosphorodiamidate **3.58** under vigorous conditions followed by conversion to the nonaflate **3.59** and cross coupling of the latter compound allowed the construction of the 1,2,4,- substituted aromatic **3.60**.

Other practical applications of phosphorodiamidates and the anionic *P-ortho*-Fries rearrangement are illustrated in the synthesis of new chiral *o*-hydroxylaryl phosphoric diamides as ligands **3.61-3.67**.[29] These ligands have proven to be useful in the enantioselective addition of diethylzinc and cyanation of aromatic aldehydes. [30,31,32]



3.61 **3.62** **3.63** **3.64**

3.65 **3.66** **3.67**

Figure 3.2 *P*-Ligands Obtained from the Anionic *ortho P*-Fries Rearrangement of Aryl Phosphorodiamidates.

3.4. Aims of Research

Despite its high *ortho*-directing power, the $OPO(NMe_2)_2$ DMG has had relatively little impact and application in synthetic chemistry. This is most likely due to the

requirement of the unpractical metalation temperature -105 ^{o}C for this DMG to prevent the anionic P- *ortho*- Fries rearrangement, although this aspect may be overcome by the aforementioned work by Knochel. In this context, we aimed to design a phosphorus based DMG which; a) may be metalated with commercial alkyllithiums at nominal temperatures of -78 ^{o}C, b) take part not only in anionic P- *ortho*-Fries but also in *lateral* and *remote* migrations to generate uniquely substituted phosphorus compounds, and c) be easily removed and/or converted into useful functionalities in a mild one step method, compatible with a range of functional groups.

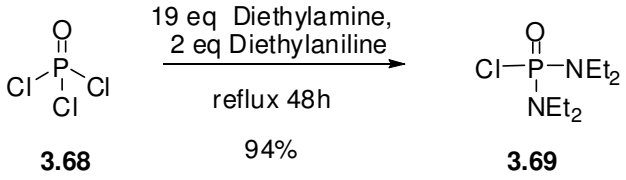
3.5. Results and Discussions

Although the anionic P-*ortho*-Fries rearrangement has been demonstrated to be synthetically useful (*vide supra*), the requirement of temperatures of -105 ^{o}C to allow quenching of the aryl anion with an external electrophile is costly and unpractical on larger scales thus diminishing its utility for the synthesis of aromatic phosphorus derivatives. The strategy of Knochel,[28] using the less reactive and more sterically hindered $TMP_2MgCl{\bullet}2LiCl$ base, suffers from slow reaction times, cost, and low solubility. An alternative approach is the structural modification of the DMG itself by analogy of the *O*-carbamate DMG for which it is well appreciated that the size of the N alkyl groups (Me, Et, ^{i}Pr) has little effect on directing power but considerably diminishes the reactivity of the electrophilic center as a function of increasing steric hindrance, inhibiting the *ortho* Fries rearrangement.[33]

Based on these precedents, Dr. Alessi[34] in our group began experimenting with the diethylphosphorodiamidate group $OPO(NEt_2)_2$ (OPAm) as a DMG under the hypothesis that the increased steric hindrance would prevent the anionic P-*ortho*-Fries migration and allow the introduction of an external electrophile at standard metalation temperatures -78 °C.

3.5.1 The Synthesis of Phenyl *N*,*N*,*N*',*N*'-Tetraethylphosphorodiamidates

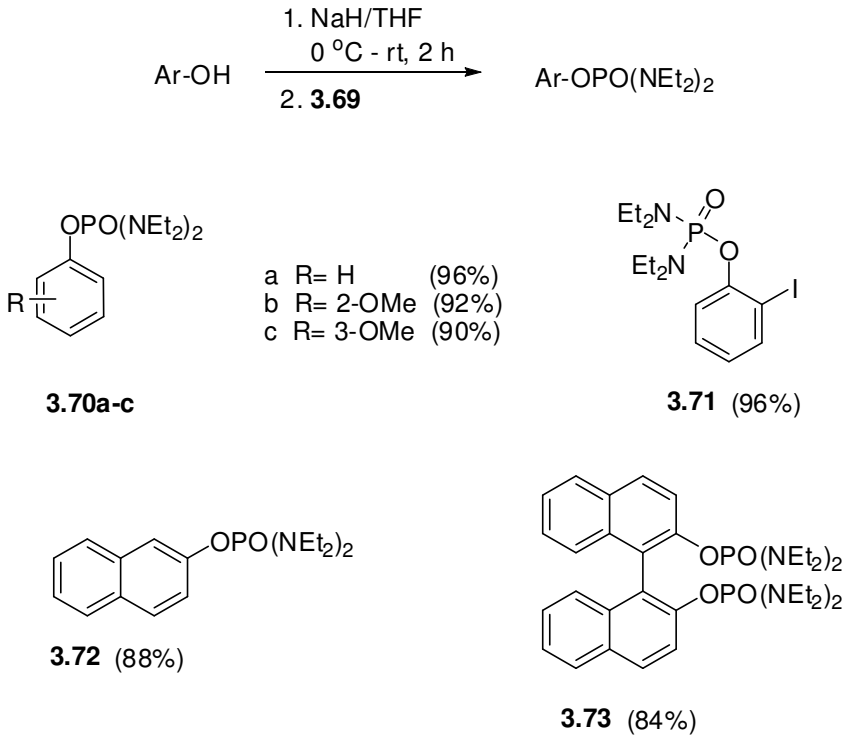
Aromatic phosphorodiamidates are most easily constructed by reaction of phenols with tetraalkylphosphorodiamidic chloride ($ClPO(NR_2)_2$), commercially available for R= Me, Et. Although commerically available, $ClPO(NEt_2)_2$ was easily synthesized on preparative scales by reaction of $POCl_3$ and diethylamine as developed Oleg Demchuk[35] (Scheme 3.9).



Scheme 3.9 Preparation Tetraethylphosphorodiamidic Chloride.

Aromatic phosphorodiamidates were prepared by reaction of phenols with a sodium hydride in THF, followed by quench with **3.69** to produce aryl phosphorodiamidates **3.70-3.73** in good yields (Scheme 3.10). Although 2-iodo-phosphorodiamidates **3.71** is also easily prepared via D*o*M, this method on 2-iodophenol is undemanding and allows the production of **3.71** in large scale. Compound **3.73** is of

interest as a substrate for double metalation-electrophile quench and anionic P-*ortho* Fries rearrangement, reactions which would produce a ligand scaffold similar to **3.67**.

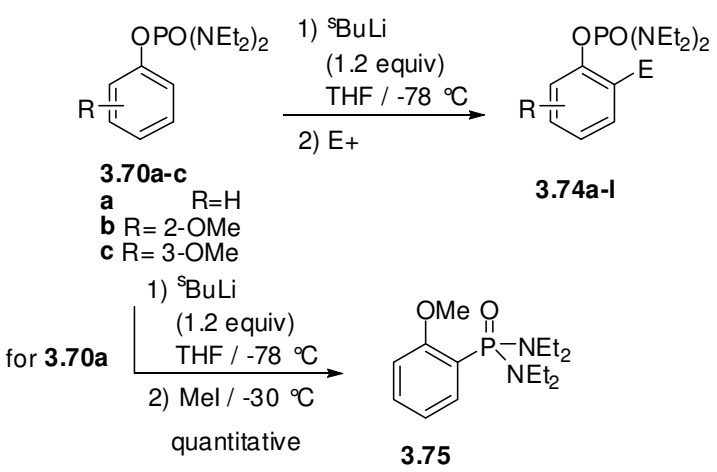


Scheme 3.10 Preparation of Various Aryl *O*-Phosphorodiamidates.

3.5.2 DoM on Aryl *O*-Phosphorodiamidates

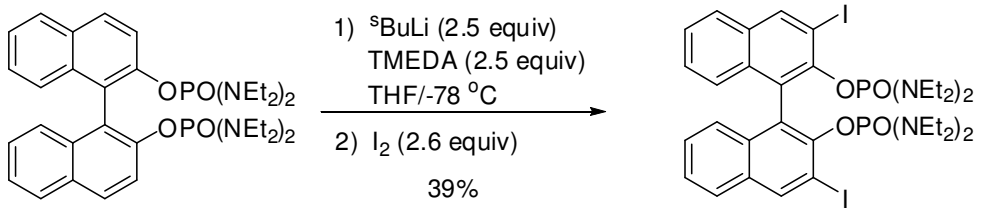
The first metalation of **3.70a** with ^{s}BuLi for 1 h at -78 ^{o}C in THF followed by quench of TMSCl gave **3.74a** in 84% yield as first demonstrated by Alessi[34] (Scheme 3.11). None of the anionic *P-ortho*-Fries rearrangement was detected, demonstrating the stability of the *ortho*-lithiated species of **3.70a** at nominal metalation temperature of -78 ^{o}C and the first successful *ortho* lithiation of the $OPO(NEt_2)_2$ group. The *o*-lithio-

intermediate was found to be stable to -30 °C, at which temperature the anionic *P-ortho*-Fries rearrangement was found to occur producing, upon quench with MeI, the *o*-methoxylaryl phosphoric diamide **3.75** in quantitative yields. The expansion and generalization of this methodology was accomplished with a variety of electrophiles affording substituted derivatives **3.74a-l**.[36]



3.74	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	6-OMe	Me	88
j	6-OMe	TMS	86
k	3-OMe	Me	84
l	3-OMe	I	84

* isolated as pinacol ester



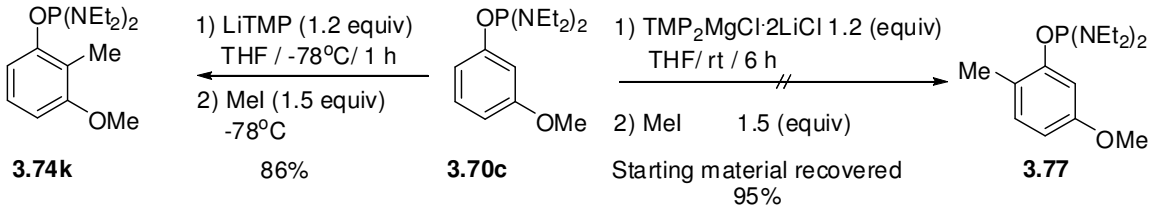
3.73 **3.76**

Scheme 3.11 DoM on Aryl *O*-Phosphorodiamidates.

The double metalation-iodination of **3.73** was accomplished but the reaction suffered from low yields due to problems in purification of the mono- versus the bis-

iodinated **3.76** products. Compound **3.76** is an attractive molecule because it allows further construction of potentially interesting phosphorodiamidate ligand scaffolds.

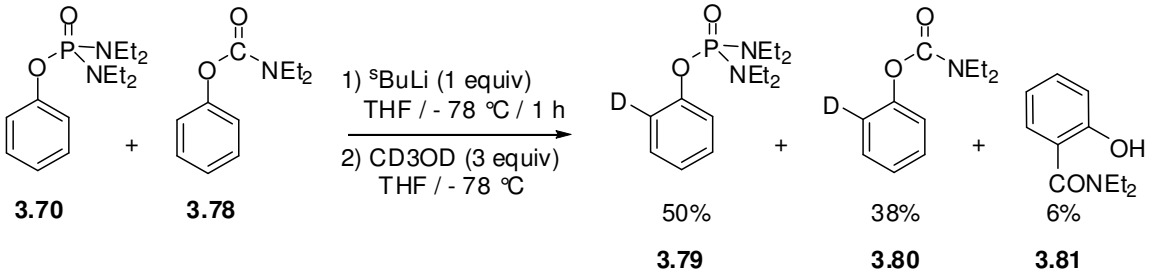
Similar to Watanabe`s work, metalation of **3.70c** with ^{s}BuLi was found to occur at C-2, between the two DMGs, due to the synergistic effect of the OPAm and methoxy groups. Knochel showed that with bulkier TMP based organomagnesium bases, metalation commonly occurs at the C-6 position. Provided with the opportunity to tune the selectivity of metalation by choice of base, **3.70c** was treated with LiTMP (Scheme 3.12). Disappointingly, metalation was found to occur at the C-2 position to produce, upon treatment with MeI, **3.74k**, which constitutes the same regioselectivity as that obtained by using ^{s}BuLi. In an effort to effect metalatation at the C-6 position, **3.70c** was treated with $TMP_2MgCl{\cdot}2LiCl$ followed by quench with MeI. Unfortunately, no metalation was observed even at room temperature and starting material was recovered in 95% yield.



Scheme 3.12 Attempts to Change Regioselectivity with *meta* Substituted Aryl OPAm derivatives.

Assessment of the OPAm DMG coordinating ability was performed by Alessi[34] *via* an intermolecular experiment. Metalation of an equimolar mixture of **3.70a** and **3.78**

with only 1 equivalent of ^{s}Buli and subsequent quench with CD_3OD at -78 ^{o}C resulted in the formation of deuterated phosphorodiamidate **3.79** in 50% yield, the carbamate **3.80** in 38% yield, and the anionic *ortho*-Fries hydroxy amide product **3.81** in 6% yield. Taking into account experimental error, this result infers that the phosphorodiamidate is approximately equal in metalation strength to the carbamate but less prone to the anionic P-*ortho* Fries rearrangement.

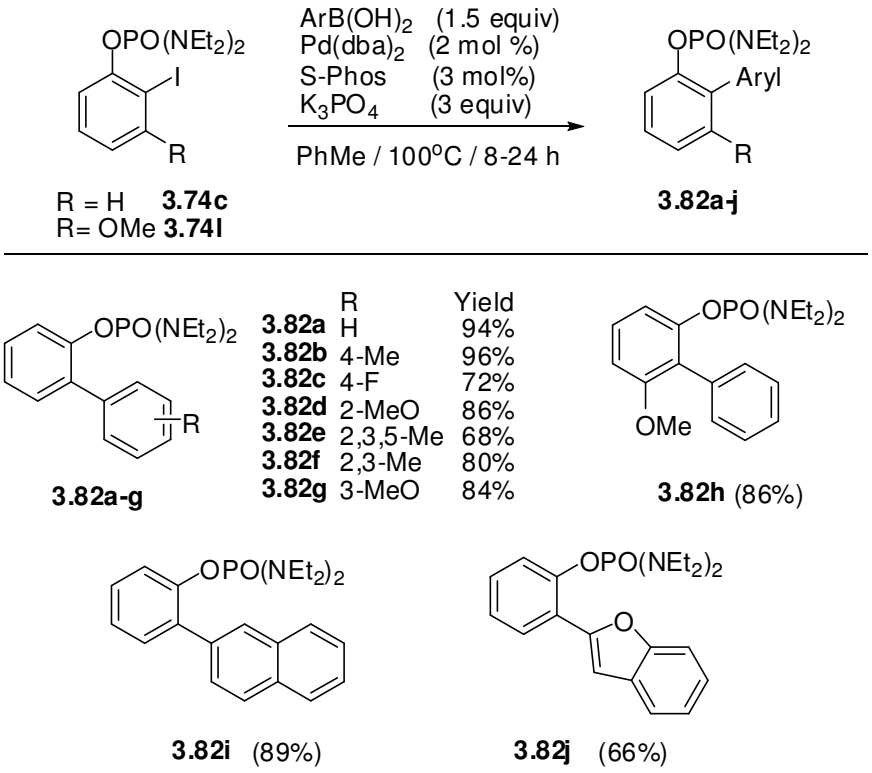


Scheme 3.13 Assessment of Coordinating Ability of the OPAm DMG.

3.5.3 Cross Coupling of *o*-Phosphorodiamidates

Considering the ease of availability of the *ortho*-iodo aryl *O*-phosphodiamidates by DoM chemistry, their exploitation as cross coupling partners was pursued. Thus, a number of biaryls were synthesized via the Suzuki-Miyaura cross coupling reaction of *o*-iodo phosphorodiamidates **3.74i,c** with a variety of aryl boronic acids furnishing the biaryls **3.82a-h** in good to excellent yields (Scheme 3.14). SPhos[16] proved to be an exceptional ligand for this reaction and was widely employed due to its high activity, allowing the preparation of sterically hindered trisubstituted biaryls such as **3.82e** (68%)

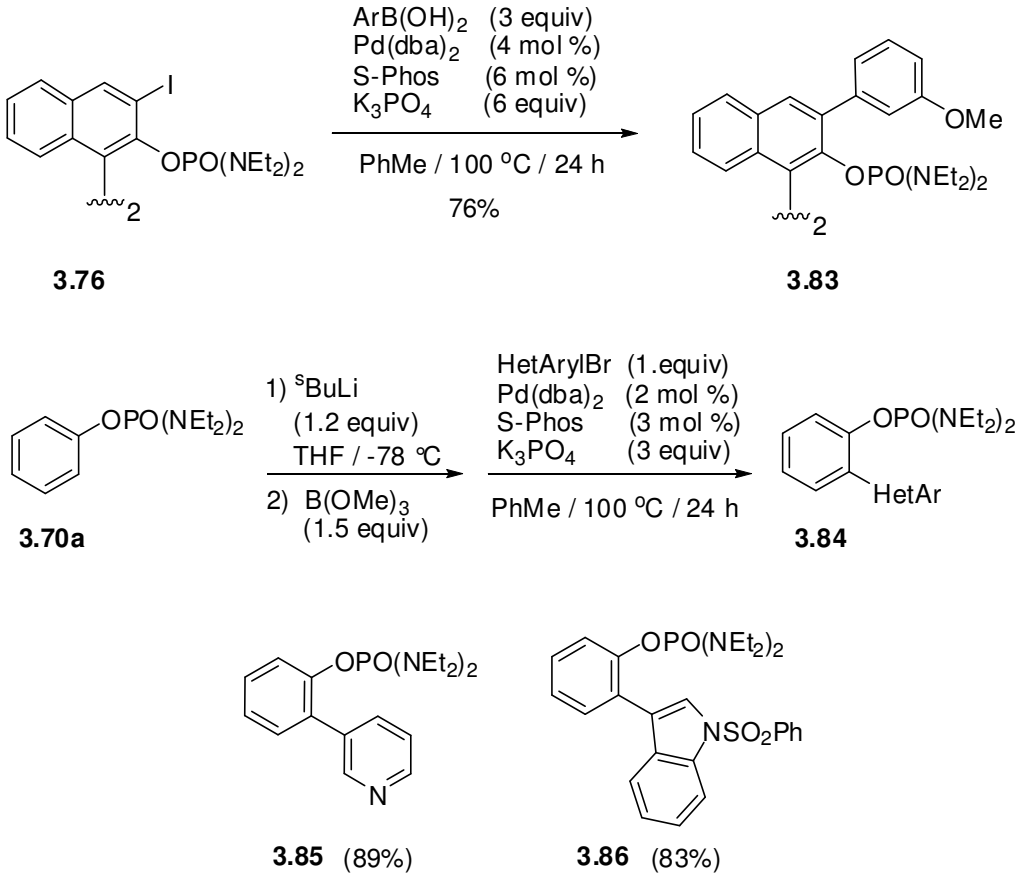
in good yields. In addition, their high reactivity allowed relatively low Pd and ligand loading, greatly facilitating the purification procedure.



Scheme 3.14 Suzuki- Miyaura Cross Coupling of *ortho*- Iodo-Aryl OPAm.

The 3,3'-bis-iodo binaphthol derivative **3.76** was found to undergo smooth cross coupling producing the bis-arylated product **3.83** in good yield (Scheme 3.15). Electron deficient boronates are known to cross couple poorly, thus the ability to invert the cross coupling partners to obtain high yields of products as demonstrated here is a valuable strategy. Given the isolation difficulties of the boropinocolate **3.74f**, the synthesis of *o*-heterobiaryls **3.84** was accomplished in a one pot manner. Thus, sequential metalation of **3.70a** and quench with trimethylborate was followed by cross coupling of the crude

intermediate boronate with 3-bromopyridine and a 3-bromoindole to furnish **3.85** and **3.86** respectively in good yields over two steps.

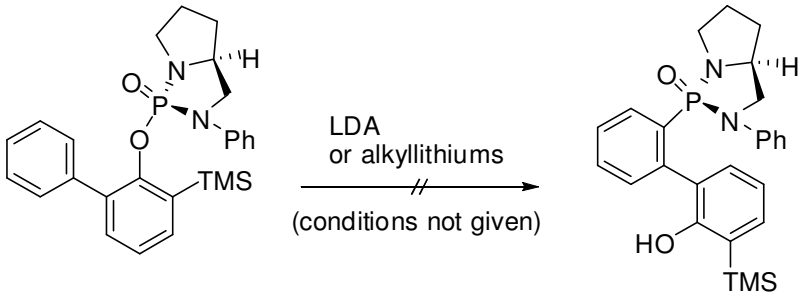


Scheme 3.15 Bis Cross Coupling of 3.76 and one Pot Synthesis of Heterobiaryls 3.85 and 3.86.

3.5.4 Directed remote Metalation (DreM) of Biaryl 2-phosphorodiamidates

Biaryl 2-*O*-carbamates and 2-amides undergo convenient Directed *remote* Metalation (DreM) reactions, allowing the construction of natural product targets and biologically relevant skeletons.[37] Unlike the anionic P-*ortho*-Fries, the DreM has not

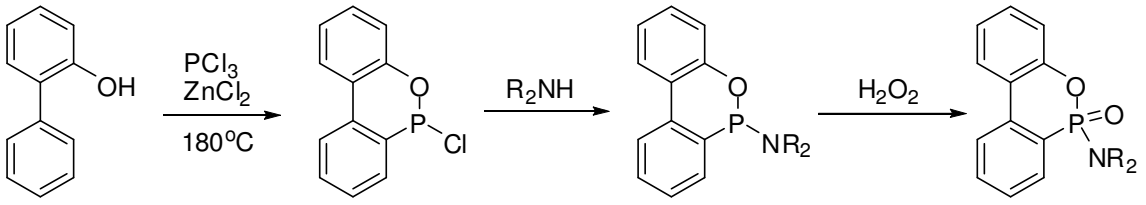
been reported for the phosphate and the phosphorodiamidate groups. Buono[29] attempted to effect this reaction on the *ortho*-silylated chiral phosphorodiamidate **3.87** (Scheme 3.16). However, the lack of any reaction upon treatment with LDA (or LDA/E^+) led him to suggest that the diazaphospholidine oxide group does not favor the involvement of a complex-induced proximity effect (CIPE).[37]



3.87 **3.88**

Scheme 3.16 DreM attempts on O-Phosphorodiamidate 3.87.[29]

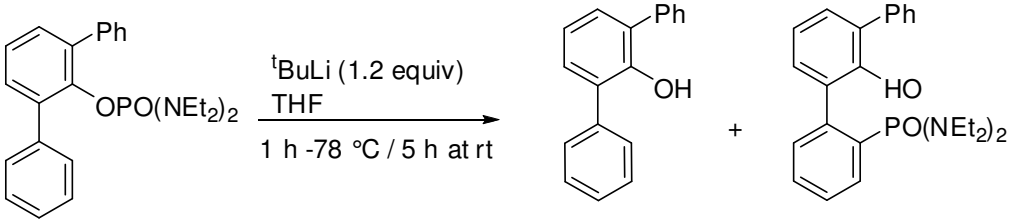
Amino-oxaphosphorine oxides of the prototype structure **3.92** are generally known compounds used as flame retardants[38] whose synthesis is accomplished by phosphorylation of the commercially available phenol **3.89** followed by Friedel Crafts cyclization to generate the chloro-oxaphosphinine **3.90** (Scheme 3.17).[39] Treatment with a secondary amine affords the amino phosphorane **3.91** whose oxidation gives the amino-oxaphosphorine oxide **3.92**. Due to the harsh conditions used, functionalized biaryl derivatives of **3.92** have not been synthesized; however, chiral amines have been incorporated for their use as chiral ligands.[39b]



3.89 **3.90** **3.91** **3.92**

Scheme 3.17 Industrial Synthesis of Amino-Oxaphosphorine oxides 3.92.

Preliminary work by Zumbansen[40] showed that DreM - migration of the $OPO(NEt_2)_2$ group in the bare diphenyl 2-OPAm system was difficult to achieve, but that the 3-phenyl derivative led to a partially successful result affording **3.95** in low yield together with **3.94**, the product of dephosphorylation, presumably by *t*-BuLi nucleophilic attack on the DMG followed by fragmentation.

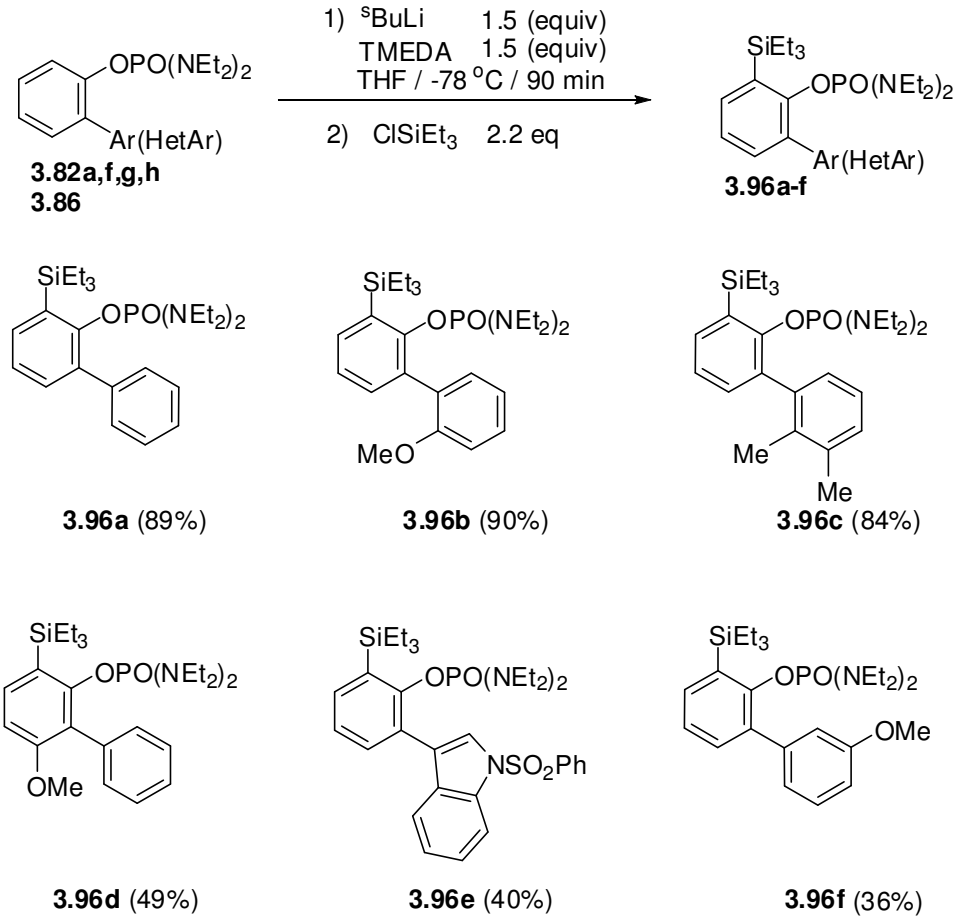


3.93 **3.94** (58%) **3.95** (32%)

Scheme 3.18 D*re*M of the $OPO(NEt_2)_2$ reported by Zumbansen.[40]

In anticipation of difficulty from the work performed by Buono and Zumbansen and the propensity of the corresponding biaryl 2-O-carbamates to undergo the anionic *ortho*-Fries rearrangement,[41] a number of the *ortho*-silylated derivatives were prepared (**3.96a-f**) in fair to good yields (Scheme 3.19). In view of the previous experience[41] and other results[42] which indicated that TMS derivatives groups undergo α-deprotonation,

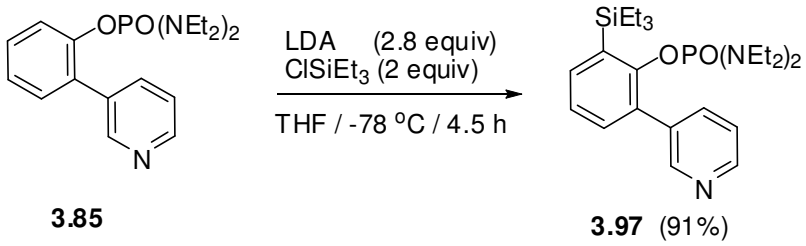
consideration was given to the TES group which is usually inert to lithium dialkylamide bases.[43] In addition, the increased steric hindrance by the bulkier silyl group was thought to "push" the $PO(NEt_2)_2$ group to the remote ring, a buttressing effect that has been observed by Schlosser and others.[44]



Scheme 3.19. Synthesis of Silylated Biaryl and Heterobiaryl O-PAm Derivatives.

The use of ^{s}BuLi for the metalation-triethyl silylation of the azabiaryl **3.85** produced **3.97** in fair yields. Although by NMR and GC-MS analysis, formation of the product was evident, it also showed the presence of an impurity which was difficult to

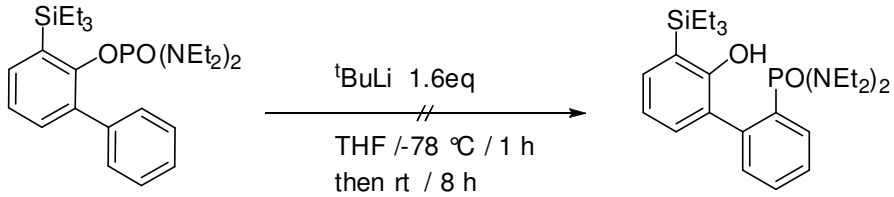
separate by column chromatography. Since C-2 nucleophilic addition of organolithium reagents pyridine has been reported,[45] the reaction was carried out with LDA 2 equivalents of TESCl which resulted in clean formation of the silylated product **3.97** (Scheme 3.20).



3.85 **3.97** (91%)

Scheme 3.20 Synthesis of Silylated Azabiaryl 3.97.

The D*re*M reaction was initially carried out on model biaryl **3.96** using the conditions of Zumbansen[35] (Scheme 3.21). Unfortunately, the desired product **3.98** was not observed by GC/MS analysis, the major products being derived from cleavage of the $PO(NEt_2)_2$ group and desilylation.

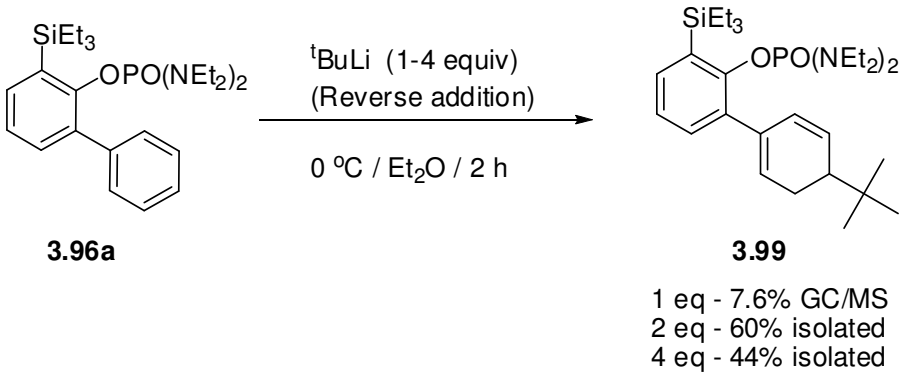


3.96a **3.98**

Scheme 3.21 Attempts to D*re*M 3.96 using reported conditions.

Not discouraged, further attempts were made in collaboration with Lampert.[46] When the attempted DreM reaction was performed in diethyl ether, it was observed that

another product appeared besides those resulting from cleavage of the $PO(NEt_2)_2$ and desilylation. Through careful reaction monitoring, it was observed that, while $PO(NEt_2)_2$ cleavage took place at -78 ^oC, the appearance of the new product occurred upon warming the reaction mixture. When the reaction was performed at 0 ^oC, in 2 hours total disappearance of the starting material and the appearance of the new product was observed. (Scheme 3.22).



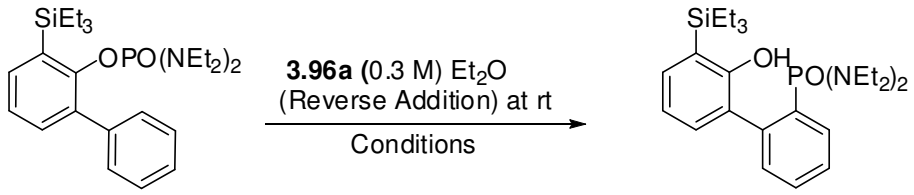
Scheme 3.22 Addition of *tert*-butyl lithium to 3.96a.

Surprisingly, isolation and extensive NMR and HRES MS confirmed (see Experimental Section) that the product of the reaction was the result of addition of ^{t}BuLi at the *para* position of the remote ring (**3.99**). It is interesting to note that at least 2 equivalents of ^{t}BuLi are necessary to generate the product in good yield while excess of this reagent is detrimental; with only 1 equivalent was used; the yield of product dropped dramatically, a result which may have mechanistic implications. To the best of our knowledge, the only analogous reaction to this result is the nucleophilic addition of ^{t}BuLi to the *para* position

of aromatic aldehydes and ketones that are pre-complexed with aluminium-tris(2,6-diphenylphenoxide).[47]

Anticipating that forcing conditions would be required to effect the desired D*re*M result, the reaction was attempted with 15 equivalents of LDA in THF at 65 ^{o}C. Gratifyingly, the product (**3.100)** was isolated in 20% yield. By careful optimization studies, it was observed that temperatures of 65 ^{o}C were required to achieve a satisfactory result. Thus, at room temperature in THF only the product of $PO(NEt_2)$ group cleavage was observed (entry 15). Strategies to inhibit cleavage products included the use of a bulkier base LiTMP, affording a slight improvement (39%, entry 12). A breakthrough resulted when TMEDA was added in the same stoichiometry as LDA which afforded dramatically increased the yield of product (63%, entry 1). All conditions using combined LDA/TMEDA showed a marked improvement in reaction yields. The use of hexanes as a solvent rather than THF allowed for completion of the reaction within 5 h with comparable yields (entry 5). Conditions (entry 2) were adapted in view of the impracticality of the conditions using of 15 equivalents of LDA/TMEDA and the low yields (31%) observed using 2 equiv of the LDA/TMEDA combination (entry 10).

Table 3.3. Optimization of the P-D*re*M Reaction.



3.96a **3.100**

No.	Base (equiv)	TMEDA (equiv)	Solvent (0.05M)	Time [h]	Temp. [°C]	Yield [%]
1	LDA 14.8	TMEDA 15	THF	22	65	63
2	LDA 4.8	TMEDA 5	Hexanes	21	65	54
3	LDA 9.8	TMEDA 10	Hexanes	6	65	52
4	LDA 14.8	TMEDA 15	THF/PhMe 1:1	22	65	51
5	LDA 14.8	TMEDA 15	Hexanes	5	65	50
6	LDA 14.8	TMEDA 5	THF	21	65	41
7	LDA 14.8	TMEDA 15	Hexanes	22	rt	39
8	LiTMP 14.8	-	THF	21	65	39
9	LDA 14.8	TMEDA 5	THF	21	65	32
10	LDA 2	TMEDA 2.2	Hexanes	22	65	31
11	LDA 14.8	-	THF	24	65	30
12	LiTMP 4.8	TMEDA 5	Hexanes	22	65	23
13	LDA 14.8	-	THF	23	65	20
14	LDA 14.8	-	THF/PhMe 1:1	22	65	14
15	LDA 14.8	-	THF	22	rt	0

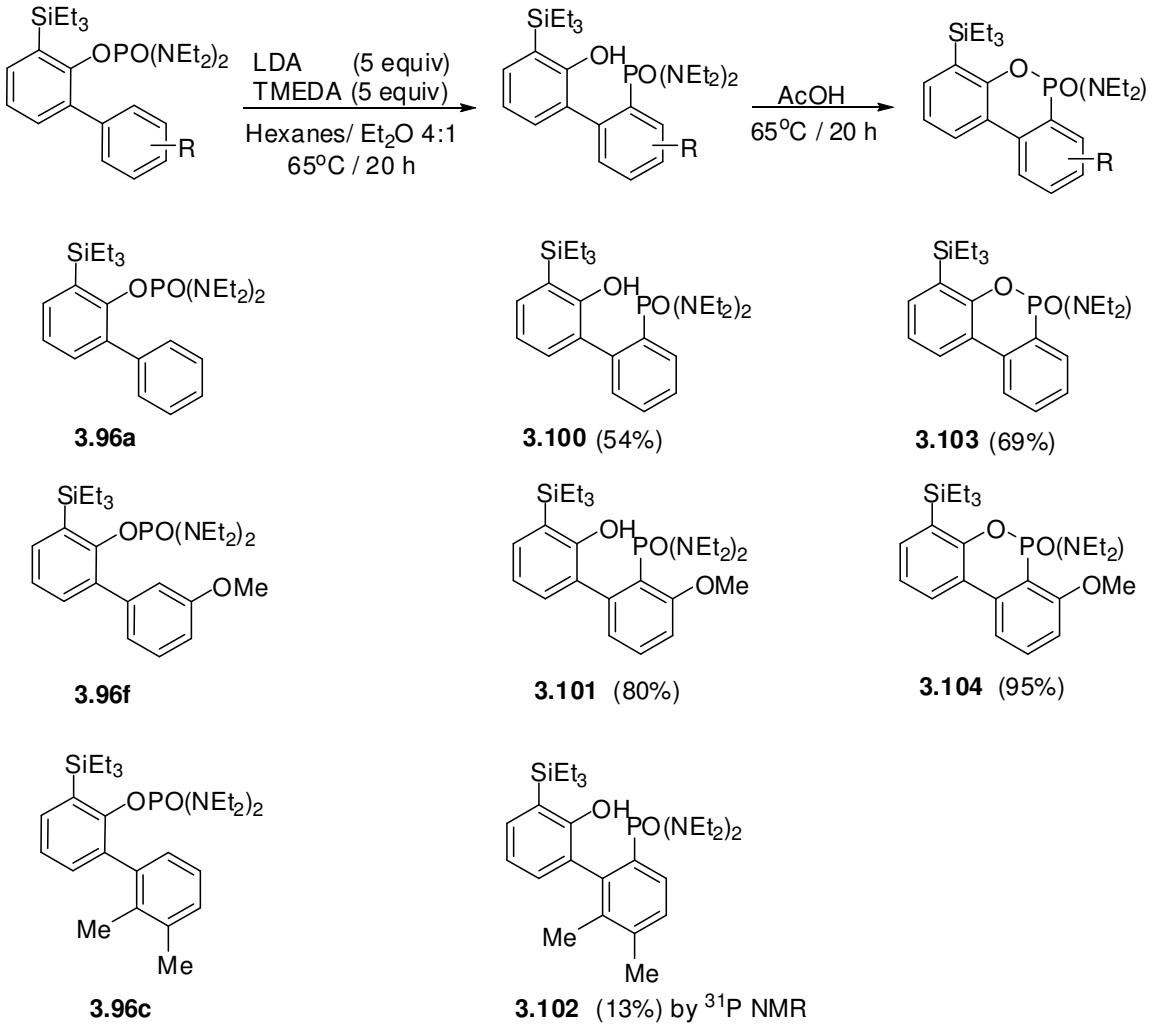
The role of TMEDA is not clear in this DreM reaction. However, in an analogous study of the anionic Snieckus-Fries rearrangement of aryl *O*-carbamates,[48] the use of additives were shown to have little effect on the yield, yet significantly enhance the rate of the reaction. TMEDA was shown to increase the reaction rate by a factor of twelve;

greater rate increases were observed with DME, TMCDA, and HMPA, additives which would be worth testing in the reaction of **3.96a**. In this case, the role of TMEDA may be to enhance the rate of the D*re*M reaction over the cleavage of the phosphorodiamidate. Counter intuitively, higher temperatures were shown to favor the D*re*M process over nucleophilic attack and cleavage. As a potential rationalization of these results, it may be envisaged that at higher temperatures the biaryl has more rotational freedom to achieve planarity, hence favoring the remote metalation process. The use of non-coordinating solvents such as hexane was observed to decrease reaction times and lessen the requirement for excess base. This may attributed to the increased stability of LDA/TMEDA at higher temperatures in hexanes, in addition to promoting the formation of dimeric LDA complexes.[49]

3.6. D*re*M Reaction for the Synthesis of Phosphonic Diamides and Their Cyclization to Amino-Oxaphosphorine Oxides

Having achieved optimization of the DreM reaction, its generalization was undertaken and led to the synthesis of a variety of new phenolic biaryl phosphonic diamides (**100-102)** (Scheme 3.23). These compounds underwent cyclization under mildly acidic conditions to give cyclic biaryl *N,N*,-diethyl amino-oxaphosphorine oxides (**103-104**). The silyl protection survived allowing possible further selective deprotection and/or *ipso*- electrophile induced substitution,[50] for later manipulation. As expected, the 3'-MeO derivative **3.96f** yielded the D*re*M product **3.101** in good yield, the result being attributed to the synergistic DoM effect of the methoxy group. Observation of an

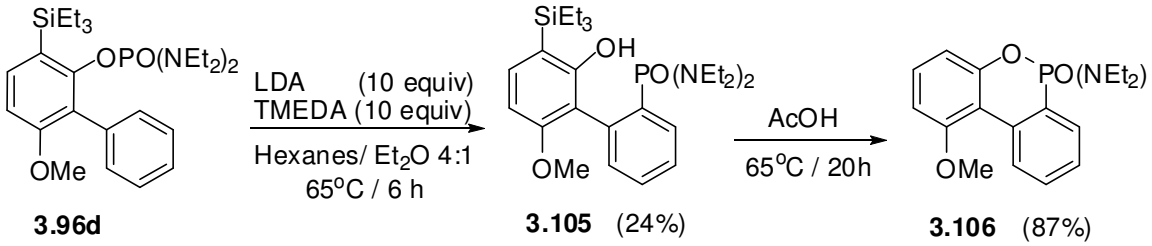
analogous tolyl-deprotonation to that achieved in 2-methyl-2'-amidobiaryls[51] for compound **3.96c** failed, producing instead the standard DreM product **3.102** in low yield.



Scheme 3.23. Generalization of the P-D*re*M reaction and Cyclization.

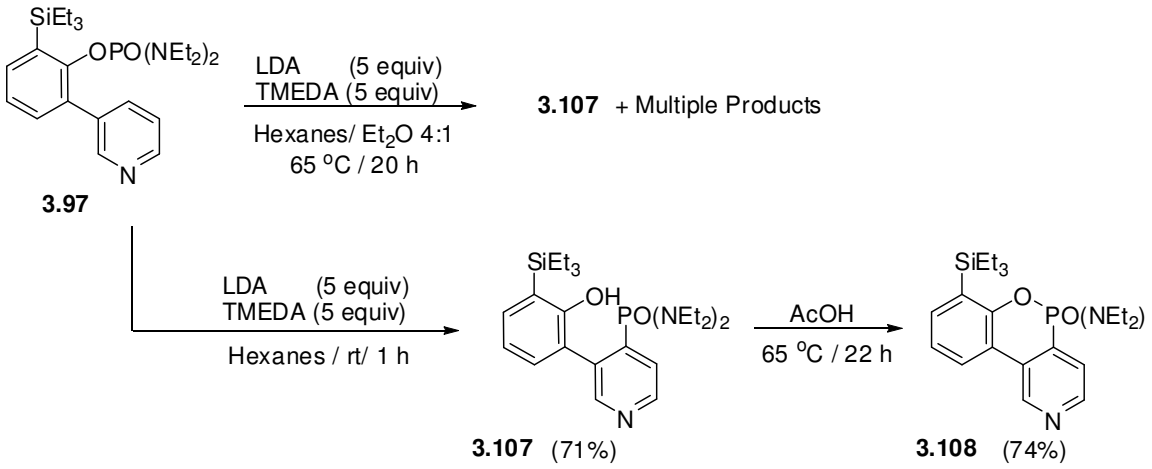
Subjecting **3.96d** to the standard DreM conditions (Scheme 3.24) resulted in the formation of multiple cleavage and desilylation products. When 10 equivalents of base was used, complete disappearance of **3.96d** was observed after 6 hours and, after workup,

the product **3.106** was isolated in low yield together with the corresponding in part due to the loss of the triethylsily group. Cyclization of **3.106** afforded **3.107** in good yield, the result of cyclization with concomitant loss of the triethylsily group. Compounds **3.106** and **3.107** are of interest due to their analogy to the Buchwald's SPhos ligand.[16]



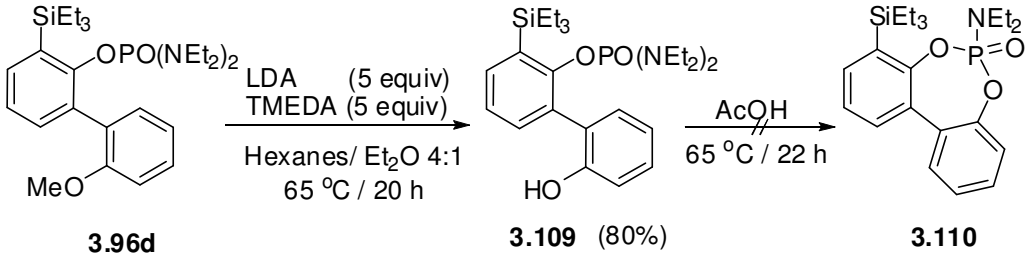
Scheme 3.24 *P*-D*re*M reaction and cyclization 2,6 di-phenolic derivatives.

When the aza-biaryl **3.97** (Scheme 3.25) was subjected to optimized DreM conditions, complete disappearance of the starting material was observed within 3 h at 65°C. The NMR of the crude product after column chromatography resembled the anionic *P*-D*re*M product **3.107**; however, it appeared to be contaminated with impurities that proved to be inseparable by column chromatography and recrystallization methods. Gratifyingly, repetition of the reaction at room temperature for 1 hour led to the isolation of the D*re*M product **3.107** in 71% yield which, upon cyclization gave the unique phosphoroamidate **3.108**.



Scheme 3.25. *P*-D*re*M and Cyclization of the azabiaryl.

The scope of the reaction of biaryl 2-OPAm derivatives was examined and it was found that not all substrates underwent the *P*-Dr*e*M. Unfortunately, the 2-methoxy derivative **3.96d** yielded the demethylated product **3.109** which could not be cyclized under acidic conditions to the resulting phosphoramidic diarylester **3.110**, possibly due to ring strain.



Scheme 3.26. Unsuccessful DreM attempt.

3.7. Conclusions

Studies conducted on the aryl *N,N,N',N'*-tetraethylphosphorodiamidate (OPAm) (**3.70a-c, 3.71-3.73**) directing metalation group (DMG) have been fruitful. First demonstrated by Alessi, the directed *ortho* metalation (DoM) reaction of these derivatives may be accomplished at nominal metalation temperatures with commercially available alkyllithiums, a significant improvement over past phosphorus based DMGs and protocols. The directing strength of the OPAm DMG was found to be comparable to that of the diethyl *O*-carbamate. On the other hand, it was found to be less susceptible to the corresponding anionic P-*ortho* Fries rearrangement, the reaction occurring at higher temperatures (approximately -30 ^{o}C) than the OAm derivative.

The resulting ortho-lithiated species of the aryl OPAm derivative may be trapped with a wide range of electrophiles to furnish a variety of 1,2- and 1,2,3- substituted aromatics (**375a-l, 3.75, 377**).[36] Suzuki-Miyaura cross coupling of the *ortho* halo and boronate aryl OPAm derivatives was demonstrated to furnish numerous biaryls and heterobiaryls (**3.82a-j, 3.83, 3.85, 3.86**) in excellent yields. The metalation ability of the derived 2-OPAm derivatives was demonstrated, by the introduction of the 3-triethylsilyl group and a series of compounds was prepared (**3.96a-f, 3.97**) to allow test of directed *remote* metalation (DreM) reactivity. Following extensive work and optimization, the DreM reaction to biaryl 2-hydroxy-2'-$PO(NEt_2)_2$ and their subsequent cyclization to amino-oxaphosphorine oxides was demonstrated. The scope and generality of this reaction was explored and numerous vaulted biaryl/azabiaryl phosphonic diamides

(**3.101, 3.102, 3.103, 3.105, 3.107**) and tricyclic amino-oxaphosphorine oxides (**3.103, 3.104, 3.106. 3.109**) were produced. The DreM reaction appears to be sensitive to sterics with hindered biaryl O-PAm systems, giving poor yields.

Further utility of the DMG is illustrated by the Suzuki-Miyaura cross coupling of the aryl OPAm derivative **3.72** with aryl boronic acids under Ni catalysis and their reductive cleavage using i-PrMgCl were demonstrated and are fully discussed in Chapter 4.

3.8. Experimental

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 made with CH_2Cl_2 or as KBr pellets using a BONEM FT-IR spectrophotomer. NMR spectra were recorded on a Bruker 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. Diethyl ether and THF 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. All solvents used in Pd catalyzed reaction were degassed via freeze pump thaw method under Argon. Alkyllithiums were purchased from Sigma-Aldrich and were titrated biweekly with N-benzylbenzamide to a blue endpoint. Anhydrous diisopropylamine, diethylamine, tetramethylethylenediamine, and 2, 2, 6, 6-tetramethylpiperidine (HTMP) obtained from Sigma-Aldrich were stored over KOH and under argon. 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.

General Method A: Synthesis of Aryl *N,N,N'N'*-tetraethylphosphorodiamidates

Using Flame dried glassware, under an atmosphere of Argon, the reaction vessel was charged with a stir bar and NaH (60% in mineral oil). Anhydrous hexane of the requisite amount was then cannulated slowly in while stirring the solution. After stirring the mixture for 10 minutes, stirring was halted and the resulting suspension left to settle. The hexanes were then carefully cannulated out of the flask leaving behind crystalline NaH. To this solution THF with the corresponding phenol (0.1-0.2 M) was added at 0^oC sequentially via cannula while stirring, the reaction was vented to allow for the release of the evolved hydrogen gas. After complete addition the reaction was allowed to warm to rt, and left for 2-3 hours. The reaction vessel was then cooled down to 0^oC using an ice bath, and the addition of $ClPO(NEt_2)_2$ was then added dropwise. The reaction was monitored and typically left at rt for 24 h. Once complete disappearance of the starting material was observed by TLC and by GC/MS the reaction was carefully quenched with the minimum amount of NH_4Cl aq at 0^oC degrees to ensure complete neutralization of any excess NaH. The stir bar was then removed and washed with a minimum amount of ethyl acetate and THF was removed carefully under reduced pressure. Additional distilled water was then added to ensure complete solvation of any inorganic salts, and the reaction mixture extracted by CH_2Cl_2 typically three times. The collected organic phases were dried under anhydrous sodium sulfate and solvent was removed under

reduced pressure. In most cases purification was performed using Kruger Rohr distillation.

General Method B: Directed *ortho* Metalation of Aryl *N,N,N'N'*-tetraethylphosphorodiamidates

Using Flame dried glassware, under an atmosphere of Argon, was added a solution of ^{s}BuLi was added dropwise at −78 °C to a stirred solution of the aryl phsophorodiamate in anhydrous THF (≈0.1-0.2M). After stirring for 1 h at -78^{o}C, the electrophile (neat or as a THF solution) was added. The reaction mixture was stirred for 20 min then removed from the cooling bath and allowed to warm to room temperature. Standard work up purification involved quenching the reaction with saturated aqueous solution of NH_4Cl, followed by removal of THF under reduced pressure or by passive evaporation under a flow of nitrogen. Additional distilled water was then added and the mixture extracted with ethyl acetate typically 3-4 times.The collected organic phases were then dried over anhydrous sodium sulfate and concentrated under reduced pressure. In most cases purification was performed by column chromatography.

General Method C: Suzuki Cross Coupling of ortho Aryl/HetAryl *N,N,N'N'*-tetraethylphosphorodiamidates

To a flame dried vial containing a Teflon coated stir bar, was added base, catalyst/catalyst precursor, ligand, aryl halide, and aryl boronic acid under an atmosphere of nitrogen.

Degassed toluene containing the aryl tetraethylphosphorodiamidate (0.2M) was added via syringe under a stream of nitrogen. The vial was then capped and the mixture stirred at indicated temperature and monitored by GC/MS and TLC. After complete disappearance of the starting material or no further conversion to product was observed the reaction mixture was cooled to room temperature and concentrated via passive evaporation under a flow of nitrogen. Distilled water was then added and the mixture extracted with ethyl acetate typically 3-4 times. The collected organic phases were then dried over anhydrous sodium sulfate and concentrated. In all cases purification was performed by column chromatography.

In some cases larger scale reactions as indicated were performed in Schlenk flasks under using similar protocol. Solids were loaded under an atmosphere of nitrogen, the Schlenk was then capped, evacuated, and backfilled with argon. Degassed solvent was then added through the Schlenk valve under Argon, the Schlenk valve closed and the reaction stirred at the indicated temperature.

General Method D: Directed *ortho* Metalation/Silylation of Biaryl/HetAryl *N,N,N'N'*-tetraethylphosphorodiamidates

Using Flame dried glassware, under an atmosphere of Argon, was added a solution of ^{s}BuLi was added dropwise at −78 °C to a stirred solution of the phosphorodiamidate in anhydrous THF (≈0.1-0.2M). After stirring for 1 h at -78 ^{o}C, $ClSiEt_3$ was added neat. The reaction mixture was stirred for 30 minutes at -78^{o}C then allowed to warm to room

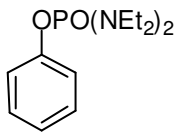
temperature. Standard work up purification involved quenching the reaction with aqueous solution of NH_4Cl, followed by removal of THF under reduced pressure or by passive evaporation under a flow of nitrogen. Additional distilled water was then added and the mixture extracted with ethyl acetate typically 3-4 times.The collected organic phases were then dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude was performed by column chromatography.

General Method E: Directed remote Metalation of biaryl/Hetaryl N,N,N'N'-tetraethylphosphorodiamidates

To a flame dried vial containing a Teflon coated stir bar was added anhydrous hexanes, diisopropylamine, TMEDA, under atmosphere argon. *n*-BuLi was added dropwise at 0 ^oC and the reaction stirred at rt for 15 min. The aryl phosphorodiamidate was added dropwise in a solution of anhydrous Et_2O (0.3 M) at 0 ^oC. The vial was then capped under argon and the solution stirred at the indicated temperatures and monitored by TLC. After complete disappearance of the starting material or 24h the reaction mixture was cooled to 0 ^oC and carefully quenched with a saturated aqueous solution of NH_4Cl and solvent was removed via passive evaporation under a flow of nitrogen. The mixture was extracted with ethyl acetate, the organic fractions collected and dried over sodium sulfate. Purification of the crude was done by flash column chromatography.

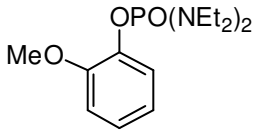
Compounds Prepared

Phenyl *N*,*N*,*N*',*N*'-tetraethylphosphorodiamidate (**3.70A**)



Prepared according to **General Procedure A** from phenol (3 g, 31.88 mmol), NaH (1.53 g, 38.26 mmol, 60% dispersion in oil) and $ClPO(NEt_2)_2$ (8.12 mL, 38.26 mmol). Standard work up and Kugelrohr distillation of the crude residue (100 °C/0.06 mmHg) afforded 8.7 g (96% yield) of **3.70a** as a clear 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.

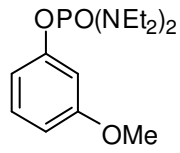
2-methoxyphenyl *N*,*N*,*N*',*N*'-tetraethylphosphorodiamidate (**3.70b**)



Prepared according to **General Procedure A** from 2-methoxy phenol (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 (110 °C/0.06 mmHg) afforded 5.58 g (92% yield) of **3.70b** 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; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, *J* = 7.9 Hz), 7.05

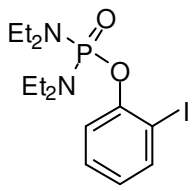
(t, 1H, J = 7.6 Hz), 6.91-6.86 (m, 2H), 3.83 (s, 3H), 3.12-3.21 (m, 8H), 1.10 (t, 12H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8 (d, J = 6.1 Hz), 140.9 (d, J =5.8 Hz), 124.3, 121.5 (d, J = 2.9 Hz), 120.7, 112.3, 55.8, 40.0 (d, J = 3.9 Hz), 39.7 (d, J = 4.8 Hz), 14.1 (d, J = 2.3 Hz), 13.5 (d, 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.

3-Methoxy - Phenyl *N*,*N*,*N*',*N*'-tetraethylphosphorodiamidate (**3.70c**)



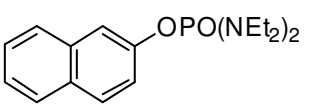
Prepared according to **General Procedure A** from 3-methoxyphenol (3.0g, 24.1 mmol), NaH (1.152 g, 28.92 mmol, 60% dispersion in oil) and $ClPO(NEt_2)_2$ (5.305 mL, 24.1 mmol). Standard work up and Kugelrohr distillation of the crude residue (125 °C/0.06 mmHg) afforded 6.8 g (90% yield) of **3.70c** as a clear oil, bp 125-130 °C/0.06 mm Hg; IR (film) V_{max} cm^{-1} 2971, 2933, 2872, 1604, 1490, 1379, 1142, 1028; ^{1}H NMR (400 MHz, $CDCl_3$,): δ *ppm*7.17 (dd, J = 10.99, 5.11 Hz, 1H), 6.82 (m, 2H), 6.64 (d, J = 8.07 Hz, 1H), 3.78 (d, J = 2.71 Hz, 3H), 3.25-3.00 (m, 8H), 1.08 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$*):*δ *ppm*160.5, 152.6, 129.6, 112.5, 109.7, 106.2, 55.4, 39.7, 14.3; ^{31}P NMR (162 MHz, $CDCl_3$*)* 14.28 (s); LRMS *m/z* (rel intensity %) 314 (M^+, 36), 299 (100), 242 (28), 191 (32), 191 (37), 72 (35); HRMS calcd for $C_{15}H_{27}N_2O_3P$ (M^+) 314.1759, found 314.1761.

2-iodo- Phenyl *N*,*N*,*N*',*N*'-tetraethylphosphorodiamidate (**3.71**)



Prepared according to **General Procedure A** from 2-iodophenol (4.03 g, 18.4 mmol), NaH (1.10 g, 27.6 mmol, 60% dispersion in oil) and $POCl(NEt_2)_2$ (5 g, 22.1 mmol). Standard work up and Kugelrohr distillation of the crude residue (135 °C/0.06 mmHg) afforded 7.24 g (96% yield) of **3.71** as a clear oil which solidified to a low melting colorless solid, mp 43-44 °C hexanes; IR (KBr) V_{max} cm^{-1}: 2969, 1578, 1467, 1231, 1027, 904, 759, 542; ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ 7.66 (d, *J* = 8.0 Hz, 1H,), 7.63 (d, *J* = 8.0 Hz, 1H,), 7.18 (dt, *J* = 7.8, 1.6 Hz, 1H), 6.71 (t, *J* = 7.6 Hz, 1H), 3.97-3.20 (m, 8H), 1.00 (t, *J* = 7.2 Hz, 12H,); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): 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, $CDCl_3$, 25°C): δ 14.2; LRMS *m/z* (rel intensity) 410 (M^+, 16), 395 (100), 337 (79), 283 (48), 218(13), 191 (59); HRMS calcd for $C_{14}H_{24}IN_2O_2P$ (M^+) 410.0620, found 410.0634.

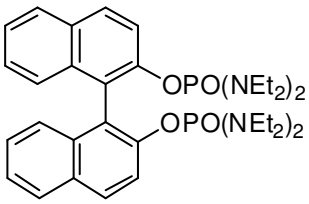
2-napthyl-*N*,*N*,*N*',*N*'-tetraethylphosphorodiamidate (**3.72**)



Prepared according to **General Procedure A** from 2-naphthol (2.66 g, 18.5 mmol), NaH (0.96 g, 24 mmol, 60% dispersion in oil) and $ClPO(NEt_2)_2$ (5 g, 22.1 mmol). Standard work up and Kugelrohr distillation of the crude residue (175-180 °C/0.06 mmHg) afforded 5.47 g (88% yield) of **3.72** as a clear oil. ^1H NMR (400 MHz, *$CDCl_3$*, 25°C) δ ppm, 7.78 (dd, J = 8.32, 4.90 Hz, 3H), 7.71 (s,

1H), 7.48-7.42 (m, 1H), 7.42-7.35 (m, 2H), 3.22-3.11 (m, 8H), 1.13-1.07 (m, 12H); ^{13}C NMR (101 MHz, *CDCl$_3$*, 25^{o}C) δ ppm, 130.4 , 129.3, 127.5, 127.4, 126.2, 124.7, 120.7, 120.7, 116.2, 116.2, 39.7, 39.7, 14.16 , 14.1; ^{31}P NMR (162 MHz, *CDCl$_3$,* 25^{o}C) δ ppm14.5 ; IR (film CH_2Cl_2) ν_{max} cm^{-1} 2971, 2932, 2872, 1622, 1591, 1505, 1461, 1380, 1359, 1242, 1211, 1196, 1172, 1146, 1101, 1027, 994, 947, 920, 824, 792, 723, 703; LRMS (EI) (*m/z)* (%), 334[M$^+$](48), 115(100), 319(85), 191(67), 69(66), 218(60), 130(56), 72(55), 143(37); HRMS (EI) calculated for $C_{18}H_{27}N_2O_2P$ [M$^+$] 334.1810: found 334.1820; b.p. 177 °C/0.06 mm

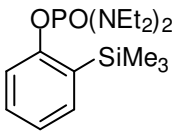
N^2,*N*^{2},*N*^{2}',*N*^{2}'-octaethyl-1-1' binaphthyl- 2',2' phosphorodiamidate (**3.73**)



Prepared according to **General Procedure A** from 2,2'binapthol (3.0g, 10.4 mmol), NaH (1.2 g, 36 mmol, 60% dispersion in oil) and $ClPO(NEt_2)_2$ (5.3 mL, 25.2 mmol). Standard work up and recrystallization of the crude material twice in hexanes afforded 5.62 g (84% yield) of **3.73** as a colourless solid. ^{1}H NMR (400 MHz, *CDCl$_3$,* 25^{o}C) δ ppm 7.94-7.88 (m, 4H),7.86 (d, J = 8.15 Hz, 2H), 7.35 (qd, J = 8.47, 4.55, 4.23, 4.23 Hz, 2H), 7.23 (d, J = 3.78 Hz, 4H),2.84 (pq, J = 9.08, 9.08, 9.08, 7.41, 7.41, 7.36, 7.36 Hz, 8H), 2.61 (t sext., J = 14.22, 14.22, 14.22, 14.22, 14.22, 7.12, 7.12 Hz, 8H), 0.87-0.78 (m, 12H), 0.67 (t, J = 7.08, 7.08 Hz, 12H); ^{13}C NMR (101 MHz, *CDCl$_3$,* 25^{o}C) δ ppm147.9, 133.7, 130.2, 129.2, 127.7, 126.3, 125.8, 124.5, 120.9, 119.6, 39.3 , 39.0, 13.7, 13.5 ; ^{31}P NMR (162 MHz, *CDCl$_3$,* 25^{o}C) δ ppm12.4; IR (film CH_2Cl_2) ν_{max} cm^{-1} 2971, 2932, 2872,

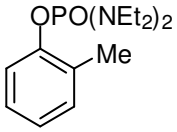
1622, 1591, 1505, 1461, 1380, 1358, 1242, 1172, 1146, 1101, 1075, 1027, 994, 974, 824, 729, 723, 694; LRMS (EI) (*m/z)* (%), 666[M^+](12), 69(100), 83(66), 97(52), 256(65), 191(48), 333(5), 403 (40), 476(38), 594(31); HRMS (EI) calculated for $C_{36}H_{52}N_4O_4P_4$ [M^+] 666.3464: found 666.3419; m.p. 109-114^{o}C (hexanes).

2-(Trimethylsilyl)phenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (**3.74a**)



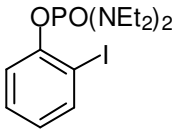
Prepared according to **general procedure B** and using **3.70a** (0.5 g, 1.76 mmol) and TMSCl (0.27 mL, 2.11 mmol) as electrophile. Standard work up and chromatography (hexanes/EtOAc 4:1) yielded 0.58 g (84%) of **3.74a** as a low melting colorless solid, mp 30-31 °C (hexanes/EtOAc); IR (film) ν_{max} 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 (**3.74b**)



Prepared according to **general procedure B** and using **3.70a** (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 **3.74b** 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.

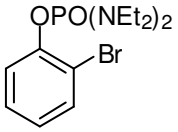
2-Iodophenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (**3.70c**)



Prepared according to **general procedure B** and using **3.70a** (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 **3.70c** as a colorless low melting solid, mp 43-44 °C (Hexanes), IR (KBr) ν_{max} cm^{-1} 2969, 1578, 1467, 1231, 1027, 904, 759, 542; ^{1}H 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, $CDCl_3$)*ppm* δ 151.7 (d, *J* = 4.4 Hz), 139.3,

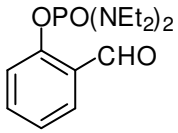
129.3, 124.9, 119.7 (d, J = 2.8 Hz), 87.9 (d, J = 9.8 Hz), 39.6 (d, J = 4.8 Hz), 14.0 (d, J = 2.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.2; MS *m/z* (rel intensity) 410 (M^+, 16), 395 (100), 337 (79), 283 (48), 218(13), 191 (59); HRMS (calcd for $C_{14}H_{24}IN_2O_2P$) 410.0620, found 410.0634.

2-Bromophenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (**3.74d**)



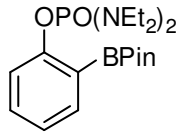
Prepared according to **general procedure B** and using **3.70a** (0.5 g, 1.76 mmol) and $(Br_2CH)_2$ (0.25 mL, 2.11 mmol) as electrophile. Standard work up and chromatography (hexanes/EtOAc 13:7) yielded 0.43 g (67%) of **3.74d** as a colourless oil, IR (film) ν_{max} cm^{-1} 2972, 1470, 1375, 1240, 1031, 792, 759, 534; ^{1}H 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 **(3.74e)**



Prepared according to **general procedure B** and using **3.70a** (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 **3.74e** 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.

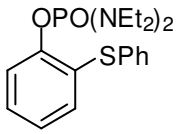
2-(boron pinacolate)-phenyl *N,N,N',N'*-tetraethylphosophorodiamidate **(3.74f)**



Prepared according to **general procedure B** and using **3.70a** (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 **3.70f** as a colorless solid, mp 62-63 (hexanes); IR (film) ν_{max} cm^{-1} 2975, 1590, 1452, 923; ^{1}H 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,

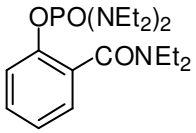
12H), 1.03 (t, 12H, *J*= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 136.8, 132.4, 123.1, 119.8 (d, *J* = 3.1 Hz), 83.4, 39.3 (d, *J* = 5 Hz), 24.9, 14.0 (d, *J* = 2.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.6; MS *m/z* (rel intensity) 410 (M^+, 1), 395 (18), 381 (26), 352 (100), 323 (23), 281 (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 **(3.74g)**



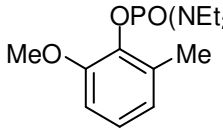
Prepared according to **general procedure B** and using **3.70a** (0.5 g, 1.76 mmol) and (after a metalation time of 2 h) PhSSPh (1.15 g, 5.28 mmol in 5 mL of anhydrous THF) as electrophile. Standard work up and chromatography (hexanes/EtOAc 3:1) yielded 0.53 g (77%) of **3.74g** as a clear oil, IR (film) ν_{max} cm^{-1} 2971, 1471, 1241, 1210, 1200, 1172, 1025, 908, 753; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.69 (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, $CDCl_3$) δ13.8; 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 (**3.74h**)



Prepared according to **general procedure B** and using **3.74a** (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 **3.74h** 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.

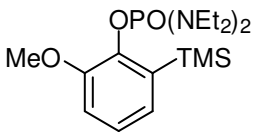
2-Methoxy-6-methylphenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (**3.74i**)



Prepared according to **general procedure B** and using **3.70b** (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 **3.74i** as a yellow oil, IR (neat) ν_{max} cm^{-1} 2981, 2363, 1474, 1210, 1023, 894, 766, 534. ^1H 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,

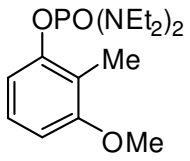
J = 7.9 Hz), 3.82 (s, 3H), 3.08-3.29 (m, 8H), 2.41 (s, 3H), 1.11 (t, 12H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 139.4, 132.1 (d, J = 3.4 Hz), 124.3 (d, J = 1.8 Hz), 123.2, 109.8, 55.6, 39.8, 17.7, 14.2 (d, J = 2.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ ppm 13.9; MS *m/z* (rel intensity): 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 (**3.74j**)



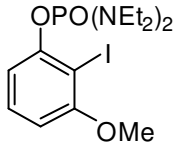
Prepared according to **general procedure B** and using **3.70b** (0.55 g, 1.76 mmol) and TMSCl (0.27 mL, 2.11 mmol) as the electrophile. Standard work up and chromatography (hexanes/EtOAc 3:2) yielded 0.58 g (86%) of **3.74j** as colourless crystalline solid, mp 76-77 °C (hexanes/EtOAc); IR (film) ν_{max} cm^{-1} 2978, 2950, 2896, 2867, 1571, 1429, 1268, 1237, 1172, 1028, 907; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 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.

3-methoxy-2-methyphenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (**3.74k**)



Prepared according to general procedure B and using **3.70c** (94.2 mg, 0.3 mmol) and MeI (22 uL, 0.39 mmol) as electrophile. Standard work up and chromatography (hexanes/EtOAc 2:1 gradient to 1:1)) yielded 88 mg (89%) of **3.74** as a colourless oil. IR (film) ν_{max} cm^{-1} 2971, 2933, 2872, 1593, 1470, 1379, 1249, 1109, 941, 792. ^{1}H NMR (400 MHz, *CDCl₃*) δ ppm 7.10 (d, *J* = 8.04 Hz, 1H), 6.99 (t, *J* = 8.25, 8.25 Hz, 1H), 6.52 (d, *J* = 8.15 Hz, 1H), 3.73 (s, 3H), 3.19-2.94 (m, 4H), 2.09 (s, 3H), 1.01 (t, *J* = 7.08, 7.08 Hz, 12H). ^{31}P NMR (162 MHz, $CDCl_3$) δ ppm 13.8. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 150.7 , 126.1, 116.8, 112.1, 105.5, 55.6, 39.6, 14.03, 9.0. MS m/z (rel intensity) 328 (52), 313.164 (100), 191 (82), 72.07 (93). HRMS (calcd for $C_{16}H_{29}N_2O_2P$) 328.1916, found 328.1916.

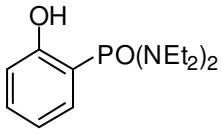
3-methoxy-2iodophenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (**3.74l**)



Prepared according to **general procedure B** and using **3.70c** (314 mg, 1.14 mmol) and I_2 (379 mg, 1.156 mmol) in 1 mL THF as electrophile. Standard work with the mofidication of the use an aqueous solution of sodium thiosulphate and chromatography (hexanes/EtOAc 2:1 gradient to 1:1) yielded 421mg (84%) of **3.74l** as a light yellow oil. IR (film) V_{max} cm^{-1} 2971, 2933, 2872, 1586, 1464, 1380, 1236, 1084, 1027, 960 940. ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm7.26 (d, J = 8.30 Hz, 1H), 7.11 (t, J = 8.26, 8.26 Hz, 1H), 6.46 (d, J = 8.21 Hz, 1H), 3.75 (s, 3H), 3.09

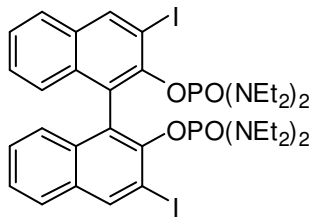
(m, 8H), 0.99 (m, 1H). 31P NMR (162 MHz, $CDCl_3$ δ ppm14.26 (s). ^{13}C NMR (101 MHz, $CDCl_3$δ ppm159.4, 153.0 , 139.3, 129.6, 112.5, 105.9, 56.6, 39.6, 14.0. LRES MS m/z (rel intensity) 440 (M+, 26), 425 48) 367 (30), 313 (100), 19 (47); HRMS (calcd for $C_{15}H_{26}N_2O_3P$, I) 440.0726 found 440.0726.

2-hydroxyphenyl *N*,*N*,*N*',*N*'-tetraethyl-phosphonic diamide (**3.75)**



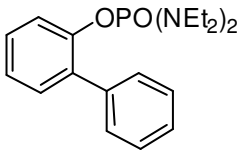
Prepared according to **general procedure B** and using **3.70a,** with the modification that no external electrophile was added and the reaction mixtured warmed from -78°C to room temperature. Obtained in quantitative yield as a clear oil, IR (neat) ν_{max} cm^{-1} 2974, 2932, 2873, 1576, 1453, 1301, 1251, 1206, 1128, 1021, 950, 762, 705; ^1H 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.

2-methoxy-6-(trimethylsilyl)phenyl *N*,*N*,*N*',*N*'-tetraethylphosphordiamidate (**3.76**)



A flame dried flask was filled with **3.76** (2 mmol, 1.33 g) in 50 ml dry THF. s-BuLi (2.5 eq, 5 mmol, 4 mL) was added dropwise at - 78 C. The mixture was stirred for 90 min at – 78 °C and then quenched with I_2 (1.2 eq, 708 mg in 10 mL THF). The temperature was raised to rt over 2h. After the quench with sat NH_4Cl, the whole was extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated to dryness. The crude mixture was purified by flash column chromatography (hexanes / ethyl acetate in a gradient 5:1 / 1:1) to give a yellow solid (712 mg, 0.775 mmol, 39 % yield). ^{1}H NMR (400 MHz, *Acetone)* δ ppm8.68 (s, 1H), 7.94 (d, *J* = 8.21 Hz, 1H), 7.46 (s, 1H), 7.33-7.20 (m, 1H), 7.04 (d, *J* = 8.60 Hz, 1H), 3.22 (m, 4H), 2.03-1.76 (m, 4H), 1.15 (t, *J* = 7.04, 7.04 Hz, 1H), 0.64 (t, *J* = 7.10, 7.10 Hz, 6H). ^{13}C NMR (101 MHz, *Acetone*) δ ppm149.2, 140.8, 134.3, 132.4, 128.0, 126.6, 126.5, 125.8, 91.53, 40.91 (dd, *J* = 15.12, 5.02 Hz,), 14.22 (dd, *J* = 115.04, 1.86 Hz). ^{31}P NMR (162 MHz, *Acetone*) δ ppm9.58. EI HRMS calcd for $C_{36}H_{50}I_2N_4O_4P_2$ 919.1474, found 919.1469.

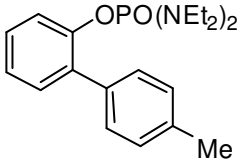
2-Biphenyl – *N,N,N',N'* –tetraethylphosphorodiamidate (**3.82a**)



Prepared according to **general procedure C** using phenyl boronic acid (55 mg, 0.45 mmol), $Pd(dba)_2$ (7 mg, 0.007 mmol), SPhos (11 mg, 0.01 mmol), K_3PO_4-H_2O (621 mg, 0.9 mmol), and **3.74c** (123 mg, 0.3 mmol) in 1.5 mL of toluene (anhydrous, degassed). The reaction mixture was stirred at 100 ^{o}C and after 8 hours the total disappearance of the starting material was

observed. After standard workup, purification the crude mixture using a gradient elution of 30% - 50% (EtOAc / hexane) over 200 mL to afford the product (102 mg, 0.28 mmol, 94%) as a clear viscous oil. IR (neat) ν_{max} 3053, 2979, 2305, 1264 cm^{-1}; ^{1}H NMR (400 MHz, *$(CD_3)_2CO$*, 25 ^{o}C): δ ppm7.61 (dd, *J* = 5.18, 3.13 Hz, 2H), 7.49 (m, 3H), 7.45-7.32 (m, 2H), 7.27 (dt, *J* = 7.43, 7.42, 1.15 Hz, 2H), 2.89-2.71 (m, 4H), 2.69-2.44 (m, 4H), 1.05-0.93 (m, 15H), 0.87 (t, *J* = 7.04, 7.04 Hz, 12H); ^{13}C NMR (101 MHz, *$((CD_3)_2CO$*, 25 ^{o}C*)*: δ ppm151.3 (d, *J* = 6.75 Hz), 139.4, 136.1 (d, *J* = 1.89 Hz), 135.1 (d, *J* = 3.49 Hz), 132.6 (d, *J* = 2.50 Hz), 131.6, 129.8, 128.1, 126.8, 124.1 (d, *J* = 1.71 Hz), 39.4, 13.6 (d, *J* = 18.62 Hz), 7.4, 4.5; ^{31}P NMR (162 MHz, *$((CD_3)_2CO,$* 25 ^{o}C) δ ppm13.2 (s); LRMS (EI, 70eV) *m/z* (%) 360 (20), 345 (100), 288 (50); EI^{+}-HRMS calcd for $C_{20}H_{29}N2O_2P$ (M^{+}): 360.1967, found 360.1969.

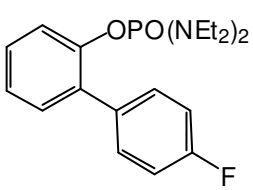
4'-Methyl-biphenyl-2- *N,N,N',N'* - tetraethylphosphorodiamidate (**3.82b**)



Prepared according to **general procedure C** using 4-Methyl-phenyl boronic acid (60.7 mg 0.45 mmol),), $Pd(dba)_2$ (7 mg, 0.007 mmol), SPhos (11 mg, 0.01 mmol), K_3PO_4-H_2O (621 mg, 0.9 mmol), and 1 mL of **3.74c** (123 mg, 0.3 mmol) in toluene (anhydrous, degassed). The reaction mixture was stirred at 100 ^{0}C and monitored by TLC and GC / MS. After 20 hours the total disappearance of the starting material was observed. The solvent was evaporated and 1 mL of distilled water was added and extracted with EtOAc (5 X 1 mL). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. The crude product was

purified over silica gel column using a gradient elution of 30%- 50% EtOAc / hexane over 200 mL to afford (108 mg, 0.28 mmol, 96%) as a pale yellow viscous oil. IR (neat) ν_{max} 2974, 2865, 1483, 1286 cm^{-1}; ^{1}H NMR (400 MHz, *((CD₃)₂CO,* 25 ^{o}C): δ ppm7.58 (d, *J* = 8.52 Hz, 1H), 7.30-6.97 (m, 7H), 2.89-2.61 (m, 9H), 2.22 (d, *J* = 18.57 Hz, 3H), 2.00-1.84 (m, 2H), 0.72 (td, *J* = 23.38, 14.31 Hz, 13H); ^{13}C NMR (101 MHz, *((CD₃)₂CO,* 25 ^{o}C): δ ppm150.0, 150.0, 137.6, 136.3, 131.6, 130.2, 129.5, 128.9, 124.5, 121.4, 121.4, 40.1, 40.1, 21.19, 14.3; ^{31}P NMR (162 MHz, *((CD₃)₂CO,* 25 ^{o}C): δ ppm13.1 (s); LRMS (EI, 70eV) *m/z* (%) 374 (20), 359(100), 302(52), 288(43); EI+-HRMS calcd for $C_{20}H_{29}N_2O_2P$ (M^+): 374.2123, found 374.2128.

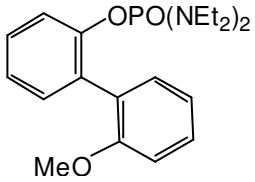
4'-Flurobiphenyl-2-*N,N,N',N'* - tetraethylphosphorodiamidate (**3.82c**) :



Prepared according to **general procedure C** using 4-fluro-phenyl boronic acid (63 mg, 0.45 mmol), $Pd(dba)_2$ (7 mg, 0.007 mmol), SPhos (11 mg, 0.01 mmol), K_3PO_4-H_2O (621 mg, 0.9 mmol), and 1 mL of **3.74c** (123 mg, 0.3 mmol) in toluene (anhydrous, degassed). The reaction mixture was stirred at 100 ^{0}C and monitored by TLC and GC / MS. After 20 hours no conversion to the product was observed. The solvent was evaporated and 1 mL of distilled water was added and extracted with EtOAc (5 X 1ml). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. The crude product was purified over silica gel column using a gradient elution of 30%- 50% EtOAc / hexane over 200 mL to afford (83 mg, 0.22 mmol, 72%) as pale yellow viscous oil. IR (neat) ν_{max} 3054, 2988, 2305, 1421, 1286

cm^{-1}; ^1H NMR (400 MHz, *((CD₃)₂CO,* 25 °C): δ ppm7.60 (d, *J* = 8.63 Hz, 1H), 7.46-7.32 (m, 2H), 7.29-7.02 (m, 5H), 2.92-2.61 (m, 8H), 0.88-0.57 (m, 12H); ^{13}C NMR (101 MHz, *((CD₃)₂CO,* 25 °C): δ ppm164.3, 150.0, 135.5, 132.894, 132.3, 131.7, 130.1, 129.3, 124.6, 121.4, 115.8, 115.6, 40.1, 14.3; ^{31}P NMR (162 MHz, *((CD₃)₂CO,* 25 °C): δ ppm13.3 (s); LRMS (EI, 70eV) *m/z* (%) 378 (20), 363 (100), 306 (50), 292 (45); EI^+-HRMS calcd for $C_{20}H_{29}N_2O_2P$ (M^+): 378.1872, found 378.1883.

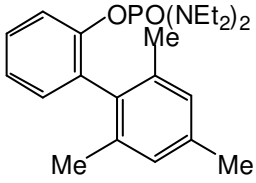
2'-Methoxybiphenyl-2- *N,N,N',N'* - tetraethylphosphorodiamidate (**3.82d**) :



Under Prepared according to **general procedure C** using 2-methoxy-phenyl boronic acid (68 mg 0.45mmol), $Pd(dba)_2$ (7 mg, 0.007 mmol), SPhos (11 mg, 0.01 mmol), K_3PO_4-H_2O (621 mg, 0.9 mmol), and 1 mL of **3.74c** (123 mg, 0.3 mmol) in toluene (anhydrous, degassed). The reaction was stirred at 100 °C and monitored by TLC and GC / MS. After 20 hours the solvent was evaporated and 1 mL of distilled water was added and extracted with EtOAc (5 X 1 mL). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. The crude product was purified over silica gel column using a gradient elution of 30%-50% (EtOAc / hexane) over 200 mL to afford (101 mg, 0.26 mmol, 86%) as yellow viscous oil. IR (neat) ν_{max} 3052, 2974, 2934, 2873, 1703, 1594 cm^{-1}; ^1H NMR (400 MHz, *((CD₃)₂CO,* 25 °C): δ ppm7.49 (d, *J* = 8.27 Hz, 1H), 7.26-7.13 (m, 2H), 7.10-6.83 (m, 5H), 3.61 (s, 3H), 2.83-2.68 (m, 9H), 0.75 (t, *J* = 7.07 Hz, 13H); ^{13}C NMR (101 MHz, *((CD₃)₂CO,* 25 °C): δ ppm158.1, 132.2, 132.0, 129.8, 128.9, 128.4, 123.7, 120.9, 120.3,

120.3, 111.6, 55.6, 40.1, 14.3; ^{31}P NMR (162 MHz, *($(CD_3)_2CO$,* 25 ^{o}C): δ ppm12.2 (s); LRMS (EI, 70eV) *m/z* (%) 390 (18), 319 (20), 318 (100), 304 (32); EI^{+}-HRMS calcd for $C_{20}H_{29}N_2O_2P$ (M^{+}): 390.2072, found 390.2070.

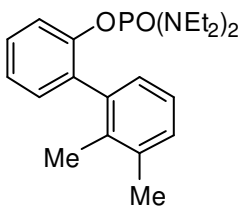
2',4',6'- Trimethylbiphenyl-2- *N,N,N',N'* - tetraethylphosphorodiamidate (**3.82e**) :



Prepared according to **general procedure C** using 2,4,6-trimethylphenyl boronic acid (74 mg 0.45mmol), $Pd(dba)_2$ (7 mg, 0.007 mmol), SPhos (11 mg, 0.01 mmol), K_3PO_4-H_2O (621 mg, 0.9 mmol), and 1 mL of **3.74c** (123 mg, 0.3 mmol) in toluene (anhydrous, degassed). The vial was capped under nitrogen, stirred at 100 ^{0}C and monitored by TLC and GC / MS. After 20 hours the solvent was evaporated and 1 mL of distilled water was added and extracted with EtOAc (5 X 1 mL). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. The crude product was purified over silica gel column using a gradient elution of 30%- 50% EtOAc / hexane over 200 mL to afford (82 mg, 0.20 mmol, 68%) as pale yellow viscous oil. IR (neat) ν_{max} 3053, 2983, 2305, 1422, 1265 cm^{-1}; ^{1}H NMR (400 MHz, *($(CD_3)_2CO$,* 25 ^{o}C): δ ppm7.35 (d, *J* = 8.29 Hz, 1H), 7.29-7.13 (m, 1H), 7.04 (dd, *J* = 10.76, 4.05 Hz, 1H), 7.00-6.88 (m, 1H), 6.78 (d, *J* = 9.98 Hz, 2H), 0.90-0.50 (m, 13H), 1.88 (d, *J* = 21.78 Hz, 6H), 2.75 (t, *J* = 7.07, Hz, 9H); ^{13}C NMR (101 MHz, *($(CD_3)_2CO$,* 25 ^{o}C): δ ppm150.4, 150.3, 137.3, 137.0, 135.8, 132.8, 132.7, 132.2, 131.7, 128.9, 128.7, 124.3, 120.6, 120.6, 40.1, 21.1, 20.7, 14.3; ^{31}P NMR (162 MHz,

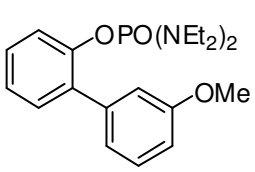
((CD$_3$)$_2$CO, 25 ^{o}C): δ ppm12.6 (s); LRMS (EI, 70eV) *m/z* (%) 402 (86), 387 (65), 330 (63), 191 (100); EI^{+}-HRMS calcd for $C_{20}H_{29}N_2O_2P$ (M^{+}): 402.2436, found 402.2444.

2',3'-dimethylybiphenyl-2- *N,N,N',N'*-Tetraethylphosphorodiamidate (**3.82f**)



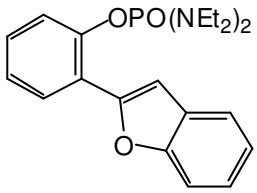
Prepared according to **general procedure C** using **3.74c (**420 mg, 1.02 mmol), 2, 3-dimethylphenyl boronic acid (233 mg, 1.53 mmol), K_3PO_4-H_2O (938 mg, 4.08 mmol), $Pd(dba)_2$ (11.73 mg, 0.02 mmol) and SPhos (12.55 mg, 0.03 mmol) in 3.5 mL toluene (anhydrous, degassed). The reaction mixture was heated to 100 °C and stirred for 6.5 h. After complete conversion (GC / MS monitoring), the mixture was cooled to rt. After 20 hours the solvent was evaporated and 1 mL of distilled water was added and extracted with EtOAc (5 X 1 mL). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (hexanes / EtOAc in a gradient 5 : 1 / 1 : 1) to give a yellow oil (315 mg, 0.813 mmol, 80 %). IR (CH_2Cl_2) ν_{max} 2971, 2933, 2873, 1494, 1467, 1381, 1242, 1212, 1196, 1100, 1027, 939, 913, 787, 765, 717; ^{1}H NMR (400 MHz, *((CD$_3$)$_2$CO,* 25 ^{o}C): δ ppm7.61 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.31 (m, 1H), 7.24 – 7.09 (m, 4H), 7.01 (d, *J* = 7.1 Hz, 1H), 3.02 – 2.71 (m, 9H), 2.33 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (101 MHz, *((CD$_3$)$_2$CO,* 25 ^{o}C): δ ppm149.5, 138.5, 136.6, 135.1, 130.7, 128.9, 128.1, 127.5, 125.1, 123.2, 119.9, 119.5, 39.2 (d, *J* = 9.81 Hz), 19.7, 16.0, 13.37 (d, *J* = 13.59 Hz); ^{31}P NMR (162 MHz, *((CD$_3$)$_2$CO,* 25 ^{o}C): δ ppm12.5 (s); EI^{+}-HRMS calcd for $C_{22}H_{33}N_2O_2P$ (M^{+}) 388.2283, found 388.2266.

3'-methoxybiphenyl *N,N,N',N'*-Tetraethyl-2-phenylphosphorodiamidate (**3.82g**)



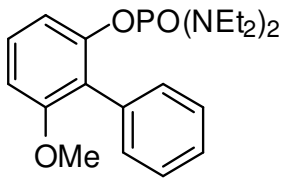
Prepared according to **general procedure C** using **3.74c** (3.00 g, 7.31 mmol), 3-methoxyphenyl boronic acid (1.67 g, 10.97 mmol), $K_3PO_4 \bullet H_2O$ (6.73 g 29.2 mmol), $Pd(dba)_2$ (83.95 mg, 0.146 mmol) and SPhos (83.9 mg, 0.219 mmol). The reaction mixture was stirred at 100 °C and after 8 hours the total disappearance of the starting material was observed (GC / MS monitoring). The mixture was cooled to rt, evaporated to remove toluene under vacuum and the resulting solution was extracted with CH_2Cl_2 (4 x 2 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash column chromatography (hexane / EtOAc 2:1) to give a colourless oil (2.40 g, 6.15 mmol, 84 %). IR (CH_2Cl_2) ν_{max} 2971, 2370, 1475, 1210, 1025, 913, 789, 719. ^{1}H-NMR (400 MHz, *((CD$_3$)$_2$CO*, 25 °C): δ ppm7.78-7.64 (m, 1H), 7.45-7.28 (m, 3H), 7.19 (t, J = 7.3, 1H), 7.05 (t, J = 4.1, 2 H), 7.01-6.88 (m, 1H), 3.85 (s, 3H), 3.09-2.88 (m, 8H), 0.94 (t, J = 7.1, 13H); ^{13}C-NMR (101 MHz, *((CD$_3$)$_2$CO*, 25 °C): δ ppm160.4, 149.9, 140.5, 134.0, 131.6, 129.9, 129.2, 124.5, 122.7, 121.4, 116.1, 113.6, 55.6, 40.1, 14.3; ^{31}P-NMR (162 MHz, *((CD$_3$)$_2$CO*, 25 °C): δ ppm13.1 (s); EI$^+$-HRMS calcd for $C_{21}H_{31}N_2O_3P$ (M^+) 390.2072, found 390.2073.

2-(Benzofuran-2-yl)phenyl *N,N,N',N'* - tetraethylphosphorodiamidate (**3.82i**)



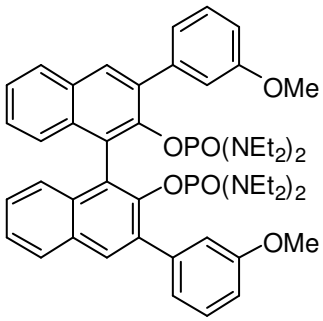
Prepared according to **general procedure C** using 2-benzofuran boronic acid (73 mg 0.45 mmol), $Pd(dba)_2$ (7 mg, 0.007 mmol), SPhos (11 mg, 0.01 mmol), K_3PO_4-H_2O (621 mg, 0.9 mmol), and **3.74c** (123 mg, 0.3 mmol) in 1.5 mL of toluene (anhydrous, degassed). The reaction was stirred at 100 ^{0}C and monitored by TLC and GC / MS. After 20 hours the solvent was evaporated and 1 mL of distilled water was added and extracted with EtOAc (5 X 1mL). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. The crude product was purified over silica gel column using a gradient elution of 30%- 50% EtOAc / hexane over 200 mL to afford (79 mg, 0.20 mmol, 66%) as a pale yellow viscous oil. IR (neat) ν_{max} 2974, 2933, 1489, 1450 cm^{-1}; ^{1}H NMR (400 MHz, *$((CD_3)_2CO$,* 25 °C): δ ppm7.83 (dd, *J* = 11.15, 8.21 Hz, 2H), 7.54 (d, *J* = 7.70 Hz, 1H), 7.44 (d, *J* = 8.19 Hz, 1H), 7.31-6.99 (m, 6H), 0.93 (dd, *J* = 14.80, 7.69 Hz, 13H), 3.03 (t, *J* = 7.07 Hz, 9H); ^{13}C NMR (101 MHz, *$((CD_3)_2CO$,* 25 °C): δ ppm130.3, 130.2, 128.5, 125.6, 124.5, 123.9, 122.1, 121.2, 121.2, 111.8, 107.0, 40.2, 14.3; ^{31}P NMR (162 MHz, *$((CD_3)_2CO$,* 25 °C): δ ppm14.7 (s); LRMS (EI, 70eV) *m/z* (%) 400 (74), 385 (25), 255 (83), 181 (100); EI^+-HRMS calcd for $C_{20}H_{29}N_2O_2P$ (M^+): 400.1916, found 400.1908.

6-methoxybiphenyl-2- *N,N,N',N'* - tetraethylphosphorodiamidate (**3.82h**)



Prepared according to **general procedure C** using phenyl boronic acid (55 mg, 0.45 mmol), $Pd(dba)_2$ (7 mg, 0.007 mmol), SPhos (11 mg, 0.01 mmol), K_3PO_4-H_2O (621 mg, 0.9 mmol), and **3.74l** (132 mg, 0.3 mmol) in 1.5 mL of toluene (anhydrous, degassed). The reaction was stirred at 100 ^oC and after 8 hours the total disappearance of the starting material was observed. After standard workup, purification the crude mixture using a gradient elution of 30%- 50% (EtOAc / hexane) over 200 mL to afford the product (101 mg, 0.26 mmol, 86%) as a clear viscous oil. IR (film) ν_{max} 2970, 2932, 2872, 1586, 1585, 1466, 1089, 1026 cm^{-1}; ^1H NMR (300 MHz, *CDCl₃,* 25 °C): δ ppm7.39 (ddd, *J* = 8.73, 5.46, 1.38 Hz, 2H), 7.36-7.27, (m, 5H), 6.75 (dd, *J* = 7.58, 1.44 Hz, 1H), 3.74 (s, 3H), 2.99-2.77 (m, 8H), 0.97-0.85 (m, 12H); ^{13}C NMR (101 MHz, *CDCl₃,* 25 °C): δ ppm157.7, 149.9, 134.1, 130.6, 129.6, 128.5, 127.7, 126.9, 112. 4, 106.2, 56.9, 39.0, 13.9; ^{31}P NMR (162 MHz, *CDCl₃,* 25 °C): δ ppm13.2 (s); LRMS (EI, 70eV) *m/z* (%) 390 (32), 375 (61), 3245 (40), 219 (73), 72 (100); EI^+-HRMS calcd for $C_{21}H_{31}N_2O_3P$ (M^+) 390.2072, found 390.2082.

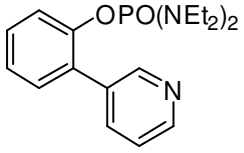
3,3'-Bis(3-methoxyphenyl)-1,1'-binaphthyl-2,2'-bis(N,N,N',N'-Tetraethyl phosphorodiamidate) (**3.83**)



A flame dried vial was charged with **3.76** (711 mg, 0.77 mmol), 3-methoxyphenylboronic acid (351 mg, 2.3 mmol), S-Phos (18.94 mg, 0.046 mmol), $Pd(dba)_2$ (17.7 mg, 0.031

mmol) and K_3PO_4-H_2O (1.06 g, 4.61 mmol) in dry toluene (5 mL). The reaction mixture was stirred at 100 °C for 19 h. After cooling to rt, the reaction was quenched with H_2O, extracted (CH_2Cl_2, 2 mL, 4 x), dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash column chromatography (hexane / EtOAc) in a gradient 2: 1 / 1 : 1) to give a colourless solid (535 mg, 0.609 mmol, 76 %). mp (hexane) 182 °C. IR (CH_2Cl_2) ν_{max} 2968, 2933, 1603, 1246, 1028, 957, 786 cm^{-1}; ^1H NMR (400 MHz, *((CD₃)₂CO)*: δ ppm8.05-7.88 (m, 2H), 7.42 (ddd, *J* = 15.62, 9.46, 4.67 Hz, 3H), 7.34-7.15 (m, 3H), 7.03-6.93 (m, 1H), 3.88 (s, 3H), 2.84-2.32 (m, 4H), 2.27-1.79 (m, 4H), 0.91-0.75 (m, 6H), 0.60 (dd, *J* = 14.30, 7.23 Hz, 6H); ^{13}C NMR (101 MHz, *((CD₃)₂CO)*: δ ppm159.3, 146.6, 141.3, 136.3, 133.7, 131.3, 130.9, 128.6, 128.2, 127.6, 125.8, 125.3, 122.7, 116.5, 112.6, 126.6, 54.7, 40.5 (d, *J* = 4.91 Hz), 39.5 (d, *J* = 5.02 Hz), 14.6 (d, *J* = 2.14 Hz), 13.7 (d, *J* = 1.87 Hz); ^{31}P NMR (162 MHz, *((CD₃)₂CO)*: δ ppm10.3 (d, *J* = 16.78 Hz), 9.5 (d, *J* = 22.66 Hz); EI^+-HRMS calcd. for $C_{50}H_{64}N_4O_6P_2$ (M^+): 879.4376, found 879.4373.

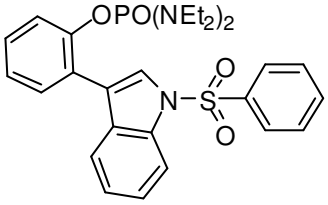
2-(pyridin-3-yl)phenyl *N,N,N',N'* - tetraethylphosphorodiamidate (**3.85**)



To a flame dried flask (25mL) containing a Teflon coated stir bar was charged with dry THF (13 mL), **3.70a** (488 mg, 1.72 mmol) and was added *s*-BuLi (1.58 mL, 2.06 mmol) at -78 °C and stirred at -78 °C. After 90 min, $B(OMe)_3$ (0.34 mL, 3.02 mmol) was added dropwise. After 40 min stirring at -78°C, the reaction was warmed to rt and quenched with NH_4Cl $_{aq.\ sat}$

(2 mL). THF was removed under reduced pressure and the aqueous solution brought to pH 2-3 with HCl. The mixture was then extracted with EtOAc (4 mL, 4 x) and the combined organic fractions were dried over Na_2SO_4. The mixture was concentrated to dryness to give a colorless solid (449 mg) in a 10mL vial. The vial and was then charged with a Teflon coated stir bar, 3-bromo pyridine (216 mg, 1.37 mmol), SPhos (17 mg, 0.041 mmol), $Pd(dba)_2$ (16.0 mg, 0.027 mmol) K_3PO_4-H_2O (901 mg, 4.11 mmol) and degassed toluene (4 mL) under an atmosphere of nitrogen. The vial was capped and the reaction was stirred at 100 ^oC for 20 h. After cooling to rt the mixture was concentrated, DI water 2mL was added and was extracted with EtOAc (4 mL, 4 x). The organic fractions were dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash column chromatography (hexane / EtOAc 1 : 1 + 10 % NEt_3) to give a yellow oil (442 mg, 1.22 mmol, 89 %). IR (CH_2Cl_2) ν_{max} 2972, 2932, 2873, 1469, 1242, 1027, 905, 714 cm^{-1}; ^1H NMR (400 MHz, *$((CD_3)_2CO$*): δ ppm8.71 (d, *J* = 1.46 Hz, 1H), 8.59 (m,1H), 7.96-7.86 (m, 1H), 7.77 (d, *J* = 8.47 Hz, 1H), 7.47 (dd, *J* = 7.69, 4.84 Hz, 1H), 7.42 (dd, *J* = 11.53, 4.52 Hz, 1H), 7.25 (t, *J* = 7.41, 7.41 Hz, 1H), 2.95 (qd, *J* = 11.27, 7.08, 7.07, 7.07 Hz, 8H), 0.94 (t, *J* = 7.09, 7.09 Hz, 12H); ^{13}C NMR (101 MHz, *$((CD_3)_2CO$*): δ ppm150.1, 149.3 (d, *J* = 5.57 Hz), 148.4, 136.6, 133.9, 130.8, 129.7 (d, *J* = 7.23 Hz,), 129.1, 123.9, 123.0, 120.5 (d, *J* = 2.90 Hz), 39.3 (d, *J* = 4.66 Hz), 13.4 (d, *J* = 2.17 Hz); ^{31}P NMR (162 MHz, *$((CD_3)_2CO$*): δ ppm13.5 (s); EI^+-HRMS calcd. for $C_{19}H_{28}N_3O_2P$ (M^+): 361.1913, found 361.1919.

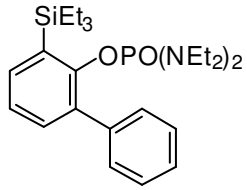
2-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl *N,N,N',N'* - tetraethylphosphorodiamidate (**3.86**)



To a flame dried dry flask (25 mL) containing a Teflon coated stir bar was charged with **3.70a** (488 mg, 1.72 mmol) in anhydrous THF (15 mL). *s*-BuLi (1.58 mL, 2.06 mmol) was added dropwise at -78 °C (dry ice / acetone) and stirred at -78 °C. After 90 min, $B(OMe)_3$ (0.34 mL, 3.02 mmol) was added and stirred at -78°C for 40 minutes. The reaction was warmed to rt and quenched with NH_4Cl sat (2 mL). THF was then removed under reduced pressure and the mixture adjusted to pH 2-3 with HCl. The mixture was then extracted with EtOAc (4 mL, 4x) and the organic fractions dried over Na_2SO_4. The mixture was evaporated to dryness to colorless solid (451 mg, 1.37 mmol) in a dried vial 10 mL. This vial was then charged with a Teflon coated stir bar, 3-bromo-1-(phenylsulfonyl)-1H-indole (459 mg, 1.37 mmol), SPhos (28 mg, 0.041 mmol), $Pd(dba)_2$ (11 mg, 0.027 mmol) and K_3PO_4-H_2O (901 mg, 4.11 mmol) in dry toluene (4 mL). The reaction was stirred at 100 °C for 20 h. After cooling to rt, the mixture was extracted with CH_2Cl_2 (20 mL, 4 x), dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash column chromatography gradient elution 30 % - 50 % (EtOAc / hexane) to give light yellow oil (613 mg, 1.14 mmol, 83 % yield). IR (CH_2Cl_2) ν_{max} 3065, 2972, 2932, 2872, 1583, 1447, 1374, 1178, 1026 cm^{-1}; ^1H NMR (400 MHz, *($(CD_3)_2CO$)*: δ ppm8.12 (dd, *J* = 7.92, 2.85 Hz, 3H), 7.85 (s, 1H), 7.82-7.70 (m, 2H), 7.64 (dd, *J* = 10.66, 4.70 Hz, 2H), 7.50 (t, *J* = 7.14, 7.14 Hz, 2H), 7.42 (ddd, *J* = 10.18, 3.82, 1.59 Hz,

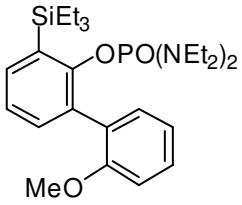
2H), 7.27 (td, *J* = 14.70, 7.60, 7.60 Hz, 2H), 2.85-2.71 (m, 8H), 0.75 (t, *J* = 7.07, 7.07 Hz, 12H); ^{13}C NMR (101 MHz, *$(CD_3)_2CO$*): δ ppm150.1, 150.0, 138.2, 134.8, 134.4, 131.3, 130.4, 129.7, 128.9, 127.0, 124.9, 124.5, 123.6, 123.5, 121.2, 120.5, 120.5, 113.5, 39.1, 13.2; ^{31}P NMR (162 MHz, *$(CD_3)_2CO$*): δ ppm13.3 (s); EI$^+$-HRMS calcd. for $C_{28}H_{34}N_3O_4PS$ (M^+): 539.2008, found 539.2008

(2-phenyl-6-triethylsilyl) *N,N,N',N'*-Tetraethyl-phenylphosphorodiamidate (**3.96a**)



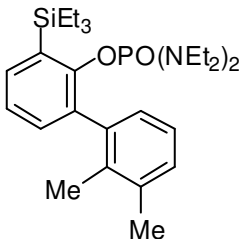
Prepared according to **General Procedure D** using **3.82a** (2.33 g, 6.47 mmol), TMEDA (1.48ml, 9.71 mmol), s-BuLi (7.71 g, 9.71 mmol) and $ClSiEt_3$ as the electrophile (1.95 mL, 11.65 mmol). Standard work up and chromatography (hexane / EtOAc 5 : 1) afforded **3.96a** as a colourless oil (2.74 g, 5.77 mmol, 89%). IR (CH_2Cl_2) ν_{max} 2964, 2872, 1397, 1382, 1251, 1210, 1170, 1027, 894, 775, 717, 700 cm^{-1}; ^{1}H NMR (400 MHz, *$(CD_3)_2CO$*): δ ppm7.61 (dd, *J* = 5.18, 3.13 Hz, 2H), 7.49 (m, 3H), 7.45-7.32 (m, 2H), 7.27 (dt, *J* = 7.43, 7.42, 1.15 Hz, 2H), 2.89-2.71 (m, 4H), 2.69-2.44 (m, 4H), 1.05-0.93 (m, 15H), 0.87 (t, *J* = 7.04, 7.04 Hz, 12H); ^{13}C NMR (101 MHz, *$(CD_3)_2CO$*): δ ppm151.3 (d, *J* = 6.75 Hz), 139.4, 136.05 (d, *J* = 1.89 Hz), 135.1 (d, *J* = 3.49 Hz), 132.6 (d, *J* = 2.50 Hz), 131.6, 129.8, 128.1, 126.9, 124.1 (d, *J* = 1.71 Hz), 39.4, 13.6 (d, *J* = 18.62 Hz), 7.4, 4.5; ^{31}P NMR (162 MHz, *$(CD_3)_2CO$*): δ ppm11.1 (s); EI$^+$-HRMS calcd. for $C_{26}H_{43}N_2O_2PSi$ (M^+): 473.2758, found 473.2753.

2-(2-methoxyphenyl)-6-triethylsilyl *N,N,N',N'*-Tetraethyl-phenylphosphorodiamidate (**3.96b**)



Prepared according to **General Procedure D** using **3.82d** (303 mg, 0.730 mmol), TMEDA (0.17 mL, 1.11 mmol), *s*-BuLi (0.90 mL, 1.11 mmol), and $ClSiEt_3$ as the electrophile (0.27 mL, 1.63 mmol) in dry THF (7 mL). Standard work up and chromatography (hexane / EtOAc 5 : 1) afforded **3.96b** as a yellow oil (337 mg, 0.666 mmol, 90%). IR (CH_2Cl_2) ν_{max} 2954, 2874, 1494, 1464, 1399, 1273, 1242, 1210, 1172, 1145, 1121, 1060, 1029, 941, 906, 776, 753, 724 cm^{-1}; ^1H NMR (400 MHz, *$(CD_3)_2CO$*): δ ppm7.46 (dd, *J* = 7.32, 1.68 Hz, 1H), 7.42-7.37 (m, 1H), 7.19 (dt, *J* = 7.43, 7.41, 1.09 Hz, 1H), 7.11-7.02 (m, 2H), 7.37-7.30 (m, 2H), 3.80 (s, 3H), 2.84-2.37 (m, 8H), 1.15-0.91 (m, 22H), 0.56 (q, *J* = 7.98, 7.97, 7.97 Hz, 5H); ^{13}C NMR (101 MHz, *$((CD_3)_2CO$*): δ ppm156.8, 152.5, 136.1, 132.7, 132.1, 131.8, 131.2, 128.7, 128.3, 123.4, 120.1, 110.6, 100.0, 99.8, 54.5, 39.7, 39.7 (d), 13.86, 7.36, 6.13, 5.72, 4.46; ^{31}P NMR (162 MHz, *$((CD_3)_2CO$*): δ ppm14.17 – 6.76 (m); EI^+-HRMS calcd. for $C_{27}H_{45}N_2O_3PSi$ (M^+): 475.2556, found 475.2546.

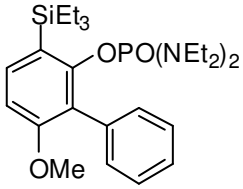
2-(2,3-dimethylyphenyl-6-triethylsilyl) *N,N,N',N'*-Tetraethyl-phenylphosphorodiamidate (**3.96c**)



Prepared according to **General Procedure D** using **3.82f** (308 mg, 0.788 mmol), *s*-BuLi (0.96 mL, 1.18 mmol), TMEDA (0.18 mL,

1.18 mmol), and $ClSiEt_3$ as the electrophile (0.29 mL, 1.73 mmol) in dry THF (7 mL). Standard work up and chromatography (hexane / EtOAc 5 : 1) afforded **3.96c** as a yellow oil (337 mg, 0.669 mmol, 85%). IR (CH_2Cl_2) ν_{max} 2954, 2874, 1459, 1396, 1236, 1210, 1175, 1117, 1077, 1028, 955, 901, 776, 735 cm^{-1}; ^1H NMR (400 MHz, *((CD₃)₂CO)*: δ ppm7.57-7.50 (m, 1H), 7.32-7.15 (m, 5H), 3.06-2.71 (m, 4H), 2.58-2.36 (m, 4H), 2.33 (s, 3H), 2.12 (s, 3H), 1.05 (m, 27H); ^{13}C NMR (101 MHz, *((CD₃)₂CO)*: δ ppm152.4, 139.4, 136.4, 135.3, 135.0, 132.4, 131.5, 129.0, 128.7, 125.3, 123.9 (d, *J* = 1.59 Hz), 40.1 (d, *J* = 8.12 Hz), 19.8, 16.4, 14.0 (d, *J* = 2.06 Hz), 7.4, 4.5; ^{31}P NMR (162 MHz, *((CD₃)₂CO)*: δ ppm11.10 (s); EI^+-HRMS calcd. for $C_{28}H_{47}N_2O_2PSi$ (M^+): 473.2748, found 473.2753.

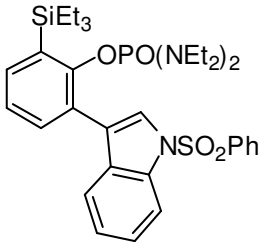
6-methoxy-3-(triethylsilyl)biphenyl-2-yl *N,N,N',N'*-Tetraethyl-phenylphosphorodiamidate (**3.96d)**



Prepared according to **General Procedure D** using 3.82h (624 mg, 1.6 mmol), *s*-BuLi (2.1 ml, 2.4 mmol), TMEDA (0.36 mL, 2.4 mmol), and $ClSiEt_3$ as the electrophile (532 uL, 4.8 mmol) in dry THF (7 mL). Standard work up and chromatography (hexane / EtOAc 5 : 1) afforded **3.96d** as colourless oil (395 mg, 0.784 mmol, 49%). IR (film) ν_{max} 2957, 2908, 2872, 1583, 1464, 1378, 1253, 1090, 1027, 956 cm^{-1}; ^1H NMR (400 MHz, *CDCl₃*): δ ppm7.42-7.21 (m, 1H), 7.16 (t, *J* = 7.20 Hz, 1H), 6.72 (d, *J* = 8.30 Hz, 1H), 3.63 (s, 1H), 2.71-2.37 (m, 1H), 1.07-0.83 (m, 1H), 0.79 (dd, *J* = 20.26, 13.27 Hz, 1H); ^{13}C NMR (101 MHz, *CDCl₃*): δ ppm156.8, 151.6, 135.8, 133.3, 131.2, 126.2, 125.6, 122.7, 122.1, 106.1, 54.8,

38.8, 13.2, 7.0, 3.7; ^{31}P NMR (162 MHz, *$CDCl_3$*): δ ppm11.28 (d, *J* = 17.80 Hz); ESI$^+$-HRMS calcd. for $C_{27}H_{45}N_2O_3PSi$ (M+H): 505.4009 found M+H 505.3036, (M+ Na) 527.3126.

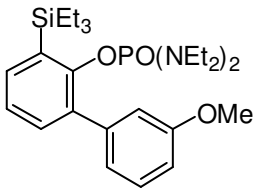
2-(1-(phenylsulfonyl)-1H-indol-3-yl)-6-(triethylsilyl)phenyl-*N,N,N',N'*-Tetraethylphosphorodiamidate (**3.96e**)



Prepared according to **General Procedure D** using **3.86** (243 mg, 0.45 mmol), *s*-BuLi (502 ml, 6.75 mmol), TMEDA (0.10 mL, 0.675 mmol), and $ClSiEt_3$ as the electrophile (0.13 mL, 0.77 mmol) in dry THF (5 mL). Standard work up and chromatography gradient elution 5:1 – 2:1 (hexane / EtOAc) over 300 ml followed by recrystallization in hexanes (1mL) afforded **3.96e** as colourless solid (46 mg, 0.07 mmol, 40%). mp (hexane): 142-144 °C; IR (CH_2Cl_2) ν_{max}; 2967, 2934, 2873, 2539, 1528, 1470, 1448, 1364, 1242, 1185, 1174, 1087 1025, 903, 734 cm^{-1}; ^{1}H NMR (400 MHz, *$((CD_3)_2CO$*): δ ppm 7.99 (d, *J* = 8.35 Hz, 1H), 7.82-7.73 (m, 2H), 7.66-7.57 (m, 1H), 7.50 (ddd, *J* = 11.73, 10.05, 4.77 Hz, 4H), 7.32 (dd, *J* = 11.06, 4.10 Hz, 2H), 7.25-7.13 (m, 2H), 7.09 (d, *J* = 7.78 Hz, 1H), 3.08-2.63 (m, 8H), 0.763 - 0.96 (m, 27H), ^{13}C NMR (101 MHz, *d6-$((CD_3)_2CO$*): δ ppm150.7 (d, *J* = 5.07 Hz), 139.0, 138.2, 137.8, 137.0, 133.8, 133.0, 132.5, 129.7, 129.2, 126.3, 125.5, 123.7, 122.7, 120.9, 119.3 (d, *J* = 3.40 Hz), 114.9 , 38.87 (d, *J* = 18.36 Hz), 13.1 (d, *J* = 9.67Hz), 7.4, 4.3; ^{31}P NMR (162 MHz, *$(CD_3)_2CO$*):

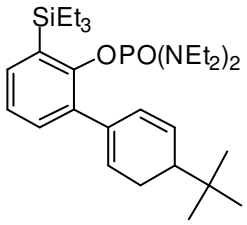
δ ppm12.4 (s); EIS$^+$-HRMS calcd. for $C_{34}H_{48}N_3O_4PSSi$ (M+H): 654.2950, found 654.2946.

2-(3'-Methoxyphenyl)-6-triethylsilylphenyl *N,N,N',N'*-Tetraethylphosphorodiamidate (**3.96f**)



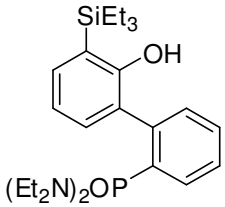
Prepared according to **General Procedure D** using **3.82g** (2.40 g, 6.15 mmol), *s*-BuLi (7.32 mL, 9.23 mmol), TMEDA (1.38 mL, 9.23 mmol), and $ClSiEt_3$ as the electrophile (1.85 mL, 11.07 mmol) in dry THF (60 mL). Standard work up and chromatography (hexane / EtOAc 5 : 1) afforded **3.96f as** a colourless oil (1.09 g, 2.16 mmol, 36 % yield). IR (CH_2Cl_2) ν_{max} 2964, 2873, 1608, 1464, 1385, 1250, 1169, 1028, 900, 775, 717 cm^{-1}; ^{1}H NMR (400 MHz, *((CD$_3$)$_2$CO)*: δ ppm7.34 (dd, *J* = 1.7, 7.3 Hz, 1H), 7.30–7.19 (m, 2H), 7.10 (td, *J* = 1.1, 7.4 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.99–6.94 (m, 1H), 6.78 (dd, *J* = 2.2, 8.0 Hz, 1H), 3.72 (s, 3H), 2.78 – 2.33 (m, 9H), 2.00–1.86 (m, 4H), 0.98–0.78 (m, 17H), 0.73 (t, *J* = 7.1 Hz, 13H); ^{13}C NMR (101 MHz, *(CD$_3$)$_2$CO*): δ ppm160.7, 152.3, 141.6, 137.1 (d), 136.0 (d), 133.5, 132.6 (d), 130.1, 125.1 (d), 123.2, 116.8, 113.1, 55.6, 40.5, 14.7 (d), 8.4, 5.4; ^{31}P NMR (162 MHz, *(CD$_3$)$_2$CO*): δ ppm11.1 (s); EI$^+$-HRMS calcd. for $C_{27}H_{45}N_2O_3PSi$ (M$^+$): 505.3009, found 505.3012.

N,N,N',N'-Tetraethyl-2-(4-tert-butylcyclohexa-1,5-dienyl)-6-(triethylsilyl)phenyl phenylphosphordiamidate (**3.99**)



To a flame dried 8 mL vial containing a Teflon coated stir bar was added anhydrous Et_2O (5 mL) and *t*-BuLi (1.03 mL, 0.6 mmol) at 0 °C under an atmosphere of argon. To this stirred solution was added a **3.96a** (1 mL, 0.3 M in Ether) dropwise while maintaining temperature at 0°C. The pale yellow solution turned dark red immediately upon the addition of **3.96a**. The reaction was stirred at 0°C and no further conversion was evident by TLC (2 h), the reaction was quenched by with satd NH_4Cl (1 mL, aqueous solution) to give immediately a colorless solution. The solution was concentrated, and the resulting solution was extracted with EtOAc (3 x 1.5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (EtOAc / hexanes 0% - 10% gradient elution) to give a colorless oil. IR (DCM) ν_{max} 3423, 2957, 2873, 1642, 1464, 1387, 1243, 1174, 1027, 896, 780 cm^{-1}. ^1H NMR (400 MHz, *$(CD_3)_2CO$*) δ ppm7.39 (dd, J = 1.8, 7.3, 1H), 7.32 – 7.22 (m, 1H), 7.14 (td, J = 1.1, 7.4, 1H), 6.35 – 6.17 (m, 1H), 6.03 (s, 1H), 5.94 (d, J = 10.2, 1H), 3.37 – 3.08 (m, 5H), 3.01 – 2.88 (m, 4H), 2.45 (dt, J = 6.7, 12.7, 1H), 2.34 – 2.15 (m, 2H), 1.10 – 0.78 (m, 27H). ^{13}C NMR (101 MHz, *$(CD_3)_2CO$*) δ ppm153.67 – 150.53 (m), 136.10 – 135.57 (m, 1C), 135.06 – 134.70 (m, 1C), 134.64 – 134.45 (m, 1C), 132.29 – 132.01 (m, 1C), 130.05 – 129.77 (m, 1C), 128.39 (s, 1C), 127.88 (s, 1C), 125.28 (s, 1C), 124.17 – 123.60 (m, 1C), 43.2 , 39.9, 32.4, 28.9, 26.8, 24.5, 13.6, 7.43, 4.6; ^{31}P NMR (162 MHz, *$(CD_3)_2CO$*) δ ppm11.6 . LRMS (EI, 70eV): 534 (3) (M+1); 533 (1) (M+); 503 (100); 475 (23). HRMS EI calcd for $C_{30}H_{55}N_2O_2PSi$ (M+) 533.3457 found 533.3459.

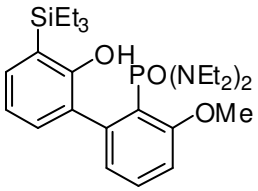
2'-hydroxy-3'-(triethylsilyl)biphenyl-2- *N,N,N',N'*-tetraethylphosphonic diamide (**3.100**)



Prepared according to **General Procedure E** using DIPA (0.22 mL, 1.5 mmol), TMEDA (0.26 mL, 1.5 mmol) and *n*-BuLi 1.47M (0.98 mL, 1.44 mmol) in 4 mL hexanes. Was added **3.96a** (1 mL, 0.3mmol) in 0.3M Et_2O. The solution was heated to (65°C) for 22 hours. Standard work up and chromatography (isocratic: CH_2Cl_2) afforded **3.101** as a white solid (76.2 mg, 0.161 mmol, 54%). mp 111°C (hexane); IR (CH_2Cl_2) ν_{max} 3050, 2957, 2875, 1584, 1465, 1382, 1210, 1023, 708 cm^{-1}. ^1H NMR (600 MHz, *$(CD_3)_2CO$*): δ ppm7.64 – 7.54 (m, 2H), 7.51 – 7.46 (m, 1H), 7.34 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.20 – 7.14 (m, 1H), 7.10 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.95 (td, *J* = 7.3, 4.2 Hz, 1H), 3.22 (dq, *J* = 11.1, 7.0 Hz, 4H), 2.91 – 2.57 (m, 5H), 1.18 (t, *J* = 7.0, 6H), 0.96 (dd, *J* = 15.4, 7.3 Hz, 9H), 0.91 – 0.79 (m, 7H), 0.64 (t, *J* = 7.1 Hz, 6H); ^1H NMR (^{31}P decoupled, 600 MHz, *$((CD_3)_2CO$*): δ ppm10.40 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.0 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 3.25 (q, *J* = 7.0 Hz, 7H), 2.92 – 2.61 (m, 7H), 1.21 (t, *J* = 7.0 Hz, 9H), 1.00 (dd, *J* = 18.7, 10.9 Hz, 11H), 0.89 (dt, *J* = 13.9, 6.9 Hz, 9H), 0.68 (t, *J* = 7.0 Hz, 9H). ^{13}C NMR (101 MHz,

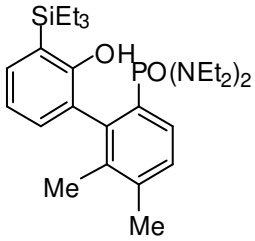
((CD$_3$)$_2$CO): δ ppm160.2, 135.8, 133.7, 133.1, 132.8, 128.0, 127.0, 120.9, 100.2, 40.5, 37.7, 14.5, 12.2, 7.14, 3.4; ^{31}P NMR (162 MHz, *((CD$_3$)$_2$CO)*: δ ppm39.22 – 29.53 (m); LRMS (EI, 70eV) *m/z* (%) 372 (100%), 375 (32%), 374 (10%); EI$^+$-HRMS calcd. for $C_{26}H_{43}N_2O_2PSi$ (M^+): 474.2831, found 474.2843.

2'-hydroxy-3'-(triethylsilyl)biphenyl-3-methoxy-2-*N,N,N',N'*-tetraethyl-phosphonic diamide (**3.101**)



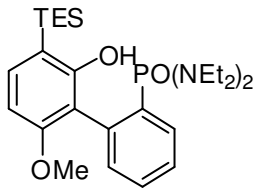
Prepared according to **General Procedure E** using DIPA (0.22 mL, 1.5 mmol), TMEDA (0.23 mL, 1.5 mmol) and *n*-BuLi (0.98 mL, 1.44 mmol) in dry hexanes (4 mL). Was added **3.96f** (1 mL, 0.3 mmol) 0.3M in Et_2O. The solution was heated to 65 °C for 5.5 h. Standard work up and chromatography (hexane / EtOAc 5 : 1) afforded **3.103** as a white solid (120 mg, 0.238 mmol, 80%). IR (CH_2Cl_2) ν_{max} 3429, 2966, 2872, 1570, 1463, 1420, 1379, 1262, 1243, 1211, 1177, 1147, 1034, 773, 730 cm^{-1}. ^{1}H NMR (400 MHz, *((CD$_3$)$_2$CO)*: δ ppm10.50 (d, *J* = 1.8 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.12 (dd, *J* = 8.1, 5.5 Hz, 1H), 7.01 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.93 – 6.80 (m, 1H), 6.63 (dd, *J* = 7.5, 3.6 Hz, 1H), 3.97 (s, 3H), 3.18 (ddd, *J* = 14.4, 10.8, 7.2 Hz, 2H), 3.12 – 3.00 (m, 2H), 2.94 (ddd, *J* = 14.3, 10.3, 7.2 Hz, 2H), 2.71 (ddd, *J* = 14.2, 9.9, 7.0 Hz, 2H), 1.12 (t, *J* = 7.1 Hz, 6H), 0.99 (dd, *J* = 12.6, 4.4 Hz, 9H), 0.93 – 0.78 (m, 7H), 0.66 (t, *J* = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, *((CD$_3$)$_2$CO)*: δ ppm27.1 (d, *J* = 16.4 Hz); EI$^+$-HRMS calcd. for $C_{27}H_{45}N_2O_3PSi$ (M^+): 504.2933, found 504.2937.

2'-hydroxy-3'-(triethylsilyl)biphenyl-3,4-dimethyl-2-*N,N,N',N'*-tetraethylphosphonic diamide (**3.102**)



Prepared according to **General Procedure E** using DIPA (0.22 mL, 1.5 mmol) and TMEDA (0.23 mL, 1.5 mmol). *n*-BuLi (0.58 mL, 1.44 mmol) in dry hexanes (4 mL). After stirring for 15 min at rt, **3.96c** (0.3 mmol, 1 mL, 0.3 M in dry diethyl ether) was added dropwise. The reaction mixture, which turned dark red immediately, was heated to 65 °C and stirred for 22 h. The reaction was quenched with NH_4Cl satd (1 mL), extracted with EtOAc (2 mL, 4 x), dried (Na_2SO_4) and the EtOAc was evaporated to dryness. 13% of the D*re*M product was found by crude ^{31}P NMR; ^{31}P NMR (162 MHz, *$((CD_3)_2CO)$*: δ ppm11.3 (s, 0.87 P), 34.4 (s, 0.13P).

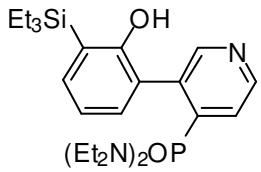
N,N,N',N'-tetraethyl-2'-hydroxy-6'-methoxy-3'-(triethylsilyl)biphenyl-2-phosphonic diamide (**3.109**)



Prepared according to **General Procedure E** using DIPA (0.72 mL, 5.0 mmol), TMEDA (0.75 mL, 5.0 mmol) and *n*-BuLi (2.23 mL, 4.8 mmol) in dry hexane (6 mL) .After stirring rt under an atmosphere of argon for min, this solution was added a stock solution of **3.96d** (1.7

mL, 0.5 mmol) (0.3 M in dry diethyl ether) was added dropwise. The solution was stirred for 20 h at 65 °C.Standard work up and chromatography gradient elution (9:1- 5:1) hexanes: ethyl acetate afforded **3.108** as a viscous oil (61 mg, ,0.12 mmol, 24%). IR (CH_2Cl_2): ν_{max} 2933, 2872, 1579, 1464, 1380, 1278, 1209, 1098, 1022, 952 cm^{-1}. ^1H NMR (400 MHz, *((CD₃)₂CO)*: δ ppmX; ^{13}C NMR (101 MHz, *CDCl₃*): δ ppm159.1, 157.1, 138.7, 138.6, 134.1, 133.2, 133.0, 130.2, 129.3, 128.5, 124.9, 124.8, 119.8, 118.8, 101.5, 38.7, 36.2, 13.1, 11.2, 6.0; ^{31}P NMR (162 MHz, *CDCl₃*): δ ppm34.2 (s); EI^+-HRMS calcd. For $C_{21}H_{30}N_2O_3P$ (M^+): 504.2937, found 504.2921.

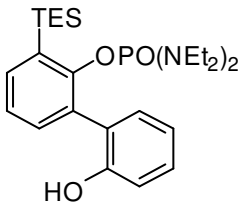
N,N,N',N'-tetraethyl-3-(2-hydroxy-3-(triethylsilyl)phenyl)pyridin-4-yl-phosphonic diamide (**3.107**)



Prepared according to **General Procedure E** using DIPA (0.22 mL, 1.5 mmol), TMEDA (0.23 mL, 1.5 mmol) and *n*-BuLi (2.52 M, 0.57 mL, 1.44 mmol) in dry hexane (4 mL) .After stirring at rt under an atmosphere of argon for 15 min, this solution was added a stock solution of **3.97** (0.7 mL, 0.3 M in dry diethyl ether) dropwise. The solution was stirred at room temperature and total disappearance of starting material was evident after 1h (TLC monitoring). Standard work up and chromatography (hexanes / EtOAc 5 : 1 +5 % NEt_3) afforded **3.108** as a colourless solid (70 mg, 0.15 mmol, 71%). mp 73-74 °C (hexane); IR (CH_2Cl_2): ν_{max} 2951, 2873, 1565, 1465, 1383, 1210, 1180, 1153, 1022, 955, 709 cm^{-1}. ^1H NMR (400 MHz, *((CD₃)₂CO)*: δ ppm10.19 (s, 1H), 8.74 (dd, *J* = 4.81, 3.69 Hz, 1H), 8.40

(d, *J* = 6.02 Hz, 1H), 7.56 (dd, *J* = 14.31, 4.89 Hz, 1H), 7.48-7.38 (m, 1H), 7.19 (dd, *J* = 7.36, 1.54 Hz, 1H), 7.05 (td, *J* = 7.37, 3.69, 3.69 Hz, 1H), 3.26 (qd, *J* = 11.32, 6.98, 6.98, 6.97 Hz, 4H), 2.76 (m., 4H) 1.23 (t, *J* = 7.00 Hz, 6H), 1.09-0.81 (m, 15H), 0.70 (t, *J* = 7.06 Hz, 6H); ^{13}C NMR (101 MHz, *$(CD_3)_2CO$*): δ ppm160.7, 153.2, 153.1, 148.8, 140.1, 138.7, 136.2, 132.8, 129.5 (d, *J* = 3.68 Hz), 128.3, 124.8, 120.3, 40.2 (d, *J* = 4.75 Hz), 37.9 (d, *J* = 5.52 Hz), 14.4, 12.3 (d, *J* = 2.42 Hz), 7.2, 3.4; ^{31}P NMR (162 MHz, *$(CD_3)_2CO$*): δ ppm30.3 (d, *J* = 16.26 Hz); EI$^+$-HRMS calcd. for $C_{25}H_{42}N_3O_2PSi$ (M^+): 476.2856, found 476.2856.

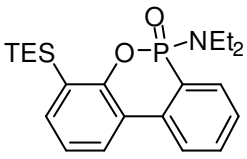
N,N,N',N'-Tetraethyl-2-(2-hydroxyphenyl)-6-triethylsilylphenylphosphorodiamidate (**3.109**)



Prepared according to **General Procedure E** using DIPA (0.22 mL, 1.5 mmol) and TMEDA (0.23 mL, 1.5 mmol). n-BuLi (0.58 mL, 1.44 mmol) in dry hexanes (4 mL). After stirring at rt for 15 min, **3.96d** (0.3 mmol, 1 mL of a 0.3 M solution in dry diethyl ether) was added dropwise and the solution was stirred for 22 h at 65 °C. A complete conversion was observed by TLC. Standard work up gave a yellow powder. The crude product was recrystallized (2 x, hexane / EtOAc 5 : 1) to give **3.110** as a white solid (121 mg, 0.24 mmol, 80%). mp (hexane / EtOAc) 206 °C. IR (CH_2Cl_2) ν_{max} 3066, 2959, 2872, 1382, 1164, 904, 777 cm^{-1}. ^{1}H NMR (400 MHz, *$(CD_3)_2CO$*): δ ppm8.48 (brs, 1H), 7.50-7.38 (m, 1H), 7.28-7.21 (m, 1H), 7.21-7.12 (m, 2H), 7.06 (d, *J* = 8.05 Hz, 1H), 6.95 (dd, *J* = 7.48, 1.64 Hz, 1H), 6.88

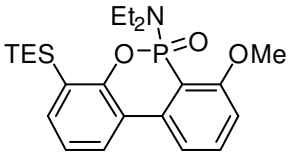
(t, J = 7.35 Hz, 1H), 2.95 (s, 6H), 2.60-2.30 (m, 3H), 0.99 (m, 27H); ^{31}P NMR (162 MHz, *((CD$_3$)$_2$CO)*): δ ppm13.8 (d, J = 22.30 Hz); EI$^+$-HRMS calcd. for $C_{26}H_{43}N_2O_3PSi$ $(M - C_2H_5)^+$: 461.2389, found 461.2386.

N,N,-diethyl-3'-(triethylsilyl)biphenyl-2-2'-oxa-aminophosphorane oxide (**3.103**)



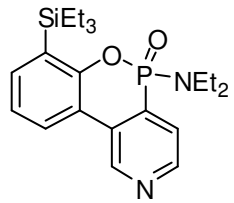
A flame dried vial was charged with **3.100** (0.20 g, 0.422 mmol) and acetic acid (glacial, 2 mL). The mixture was then stirred at 65 °C. After 22 h, the reaction was quenched with aq. Na_2CO_3 (5 mL) and the mixture was extracted with EtOAc (2 mL, 4 x), dried (Na_2SO_4) and evaporated to dryness. The crude was purified with flash column chromatography (hexane / EtOAc 2:1) to give **3.102** as a colourless solid (0.117 g, 0.29 mmol, 69%). mp (hexanes / EtOAc) 74 – 79 °C; IR (CH_2Cl_2) ν_{max} 2954, 2874, 1395, 1248, 1195, 1033, 902, 764, 727 cm^{-1}. ^{1}H NMR (400 MHz, *(CD$_3$)$_2$CO*): δ ppm8.28-8.11 (m, 2H), 7.86-7.68 (m, 2H), 7.65 -7.53 (m, 1H), 7.53-7.47 (m, 1H), 7.30 (t, J = 7.52 Hz, 1H), 3.36-3.07 (m, 4H), 1.05-0.85 (m, 15H), 1.18 (t, J = 7.07 Hz, 6H); ^{13}C NMR (101 MHz, *(CD$_3$)$_2$CO*): δ ppm155.9 (d, J = 7.70 Hz), 138.5 (d, J = 7.05 Hz), 137.7, 133.4 (d, J = 2.46 Hz), 130.3 (d, J = 9.59 Hz), 122.3 (d, J = 11.08 Hz), 124.8, 125.0 (d, J = 11.27 Hz), 125.9, 127.5 (d, J = 4.50 Hz), 129.0 (d, J = 14.39 Hz), 128.8 (d, J = 6.53 Hz), 39.6 (d, J = 4.92 Hz), 14.6 (d, J = 2.02 Hz), 7.9, 4.1; ^{31}P NMR (162 MHz, *(CD$_3$)$_2$CO*): δ ppm15.1 (s); EI$^+$-HRMS calcd. for $C_{22}H_{32}NO_2PSi$ (M^+): 372.1549, found 372.1548.

N,N,-diethyl-3'-(triethylsilyl)biphenyl-3-(Methoxy)-2-2'- oxa-aminophosphorane oxide (**3.104**)



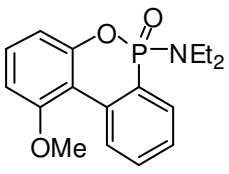
A flame dried vial was charged with **3.101** (0.120 g, 0.238 mmol) and acetic acid (glacial, 1 mL). The mixture was then stirred at 65 °C for 21 h. The reaction was quenched with Na_2SO_4 aq. (2 mL), extracted with EtOAc (2 mL, 4 x), dried (Na_2SO_4) and evaporated to dryness to give **3.104** as a colourless solid (97.4 mg, 0.225 mmol, 95%). mp (EtOAc) 114 °C. IR (CH_2Cl_2) ν_{max} = 2954, 2873, 2360, 1561, 1390, 1259, 1036, 768 cm^{-1}. ^1H NMR (400 MHz, *$(CD_3)_2CO$*): δ ppm8.11 (dd, *J* = 7.88, 1.30 Hz, 1H), 7.76 (dd, *J* = 7.85, 4.63 Hz, 1H), 7.68 (t, *J* = 8.12 Hz, 1H), 7.55-7.45 (m, 1H), 7.27 (t, *J* = 7.54 Hz, 1H), 7.15 (dd, *J* = 8.08, 5.59 Hz, 1H), 3.34 (qdd, *J* = 14.35, 9.69, 7.17, Hz, 1H), 3.14-2.96 (m, 4H), 1.02 (t, *J* = 9.40 Hz, 6H), 1.12 (m, 15H); ^{13}C NMR (101 MHz, *$(CD_3)_2CO$*): δ ppm160.7 (d, *J* = 1.92 Hz), 154.8, 138.8 (d, *J* = 4.25 Hz), 136.6, 133.5, 127.7 (d, *J* = 6.86 Hz), 127.0, 123.6, 121.0, 116.2 (d, *J* = 10.88 Hz), 115.8, 114.2, 110.1 (d, *J* = 8.05 Hz), 55.5, 39.7 (d, *J* = 6.04 Hz), 14.0 (d, *J* = 1.68 Hz), 7.1, 3.2; ^{31}P NMR (162 MHz, *$(CD_3)_2CO$*): δ ppm10.4 (s); EI^+-HRMS calcd. for $C_{23}H_{34}NO_3PSi$ (M^+): 431.2052, found 431.2056.

N,N,-diethyl-3'-(triethylsilyl)phenyl-3pyrdial-4- oxa-aminophosphorane oxide (**3.108**)



A flame dried vial was charged with **3.107** (66 mg, 0.138 mmol) and glacial acetic acid (glacial, 0.5 mL). The mixture was then heated and stirred at 65 °C. After 20 h, excess acetic acid was evaporated and the mixture was quenched with aq .Na_2CO_3 (0.5 mL), extracted with EtOAc (1 mL, 4 x), dried over (Na_2SO_4) and evaporated to dryness. The crude was purified with flash column chromatography (hexane / EtOAc gradient 20 % - 50 % + 5 % NEt_3) to give **3.109** as a colourless solid (41 mg, 0.102 mmol, 74%). mp (hexane) 96-97 ^oC. IR (CH_2Cl_2): ν_{max} 2953, 2873, 1455, 1380, 1248, 1212, 1177, 1035, 957, 902 cm^{-1}. ^1H NMR (400 MHz, *$(CD_3)_2CO$*): δ ppm9.47 (d, *J* = 6.23 Hz, 1H), 8.77 (t, *J* = 4.45 Hz, 1H), 8.34 (dd, *J* = 7.89, 1.38 Hz, 1H), 7.75-7.64 (m, 1H), 7.59 (d, *J* = 7.18 Hz, 1H), 7.38 (t, *J* = 7.54 Hz, 1H), 3.39-3.13 (m, 4H), 1.21 (t, *J* = 7.07 Hz, 6H), 1.00 (d, *J* = 1.01 Hz, 15H); ^{13}C NMR (101 MHz, *$(CD_3)_2CO$*): δ ppm155.3, 148.7 (d, *J* = 12.42 Hz), 146.1 (d, *J* = 8.89 Hz), 137.6, 133.9, 132.3, 131.8, 128.3, 126.3, 124.3, 121.9 (d, *J* = 8.22 Hz), 38.7 (d, *J* = 4.98 Hz), 13.7 (d, *J* = 1.86 Hz), 7.0, 3.2; ^{31}P NMR (122 MHz, *$(CD_3)_2CO$*): δ ppm12.3 (s); EI^+-HRMS calcd. for $C_{21}H_{31}N_2O_2PSi$ (M^+): 403,1979, found 403.1964.

N,N,-diethyl-6'-methoxy 2-2'- oxa-aminophosphorane oxide (**3.106**)



A flame dried vial was chagred with **3.105** (24 mg, 0.05 mmol) and glacial acetic acid (glacial, 0.5 mL). The mixture was then heated and

stirred at 65 °C. After 20 h, excess acetic acid was evaporated and the mixture was quenched with aq .Na_2CO_3 (0.5 mL), extracted with EtOAc (1 mL, 4 x), dried over Na_2SO_4 and evaporated to dryness. The crude was purified with flash column chromatography (hexane / EtOAc gradient 20 % - 50 %) to give **3.104** as a colorless solid (17 mg, 0.043 mmol, 87%). mp (hexane) 96-98 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ ppm8.61-8.50 (m, 1H), 7.76-7.61 (m, 1H), 7.52 (t, *J* = 7.81, 7.81 Hz, 1H), 7.35 (dt, *J* = 7.22, 7.10, 2.56 Hz, 1H), 7.20 (dd, *J* = 9.86, 6.57 Hz, 1H), 6.81 (d, *J* = 8.13 Hz, 1H), 6.74 (d, *J* = 8.30 Hz, 1H), 3.87 (s, 1H), 3.07 (ttd, *J* = 21.20, 14.37, 14.37, 7.18, 7.18 Hz, 1H), 1.07 (t, *J* = 7.05, 7.05 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm156.5, 149.2 (d, *J* = 7.7 Hz), 134.7, 129.9 (d, *J* = 2.3 Hz), 127.9, 127.4, 125.5 (d, *J* = 14.7 Hz), 111.7 (d, *J* = 5.8 Hz), 105.76, 54.4, 37.0 (d, *J* = 4.9 Hz), 12.4 (d, *J* =2 Hz); ^{31}P NMR (162 MHz, *$CDCl_3$*) 18.2 (s)

3.9. References

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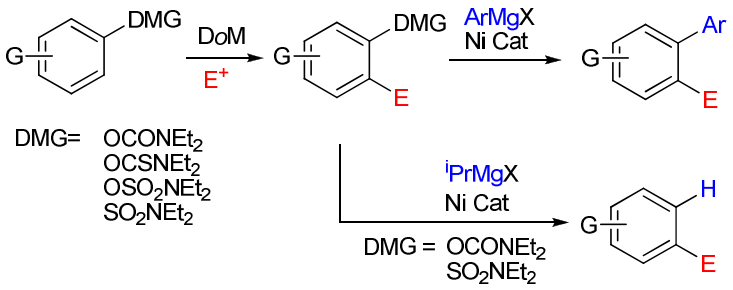
Chapter 4

Transition Metal Catalyzed Cross Coupling of Directed Metalation Groups (DMGs)

4.1 Cross Coupling of DMGs

With aims to enlarge the scope of the directed *ortho* metalation (DoM) – cross coupling strategies,[1] efforts in the Snieckus group has already established the aryl *O*-carbamate,[2] *S*-thiocarbamate,[3] sulfonamide,[4] and *O*-sulfamate[5] DMGs to undergo Grignard (Kumada-Corriu) Ni-catalyzed cross coupling reactions (Scheme. 4.1). In addition, we have demonstrated the Ni-catalyzed reductive cleavage of *O*-carbamate,[2] and sulfonamide[4a], using ^{i}PrMgCl which allows the use of these functionalities as latent directing metalation groups (DMGs), thus enhancing the scope of this chemistry for the construction of less common substitution patterns. One drawback of this method is the requirement of highly nucleophilic transmetalation partners which limits the use of many functional groups in the DMG- containing aromatic substrate.



Scheme 4.1. Cross Coupling and Excision of DMG-bearing Aromatics.

4.2 Nickel catalyzed Suzuki coupling of Phenolic Leaving Groups

For aryl-aryl bond formation, transition metal catalyzed cross coupling reactions[6] have arguably superseded all previous classical methodologies.[7] The palladium catalyzed Suzuki-Miyaura reaction[8] has proven particularly robust. For nickel catalyzed processes, cross coupling of organoboranes has been successfully achieved with a variety of leaving groups (LG = halo,[9] OTs,[10] OMs[11]). The original work of Wenkert[12] and Dankwardt,[13] followed by the seminal contributions of Chatani[14] and Kakiuchi[15] has reinforced (LG = OMe). Recently, more manipulable groups (LG = OAc,[16] OPiv[17]), functionality of significant C-O bond strength (≈106 kcal/mol)16,[18] have been introduced as cross coupling partners.

Viewed in perspective in the cross coupling area, these transformations are even more remarkable when considering the respective bond strengths of C_{aryl}-*O* versus C_{acyl}-*O*. For most the phenyl acetate derivatives, it is thought that oxidative insertion into the C_{aryl}-*O* bond proceeds though a η_2-arene or a Meisenheimer-like complex.[14] Tricyclohexylphosphine as the ligand and K_3PO_4 as the base have been prevalently used for these reactions. In addition to being a relatively inexpensive and efficient catalyst system, it is the only one that works and other phosphine/base combinations do not give even remotely comparable yields in cross coupling reactions. The proposed mechanism of this transformation by Shi[16] is illustrated (Figure 4.1) who postulated an unusual transmetalation intermediate.

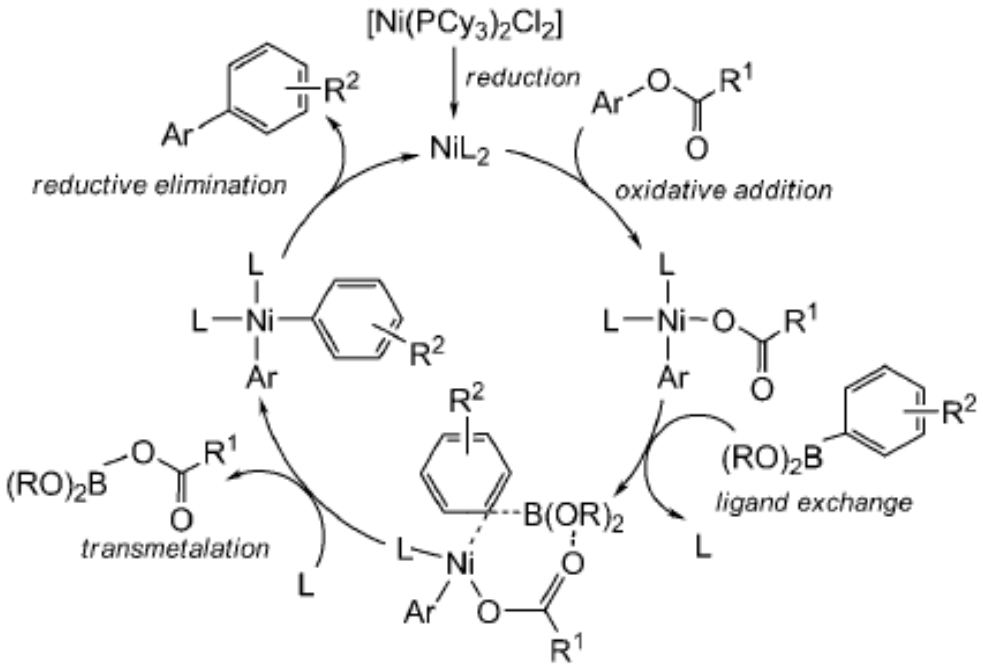
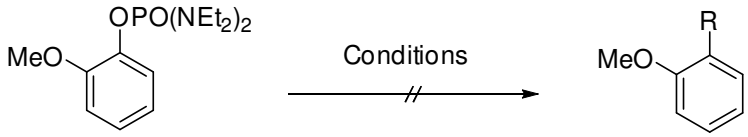


Figure 4.1. Mechanism Proposed by Shi. Reproduced from Ref.17

4.3 Aims of Research

Interest to connect the D*o*M reaction to modern methodological synthetic chemistry stimulated our efforts to further probe the potential of the $OPO(NEt_2)_2$ group as a leaving group (LG) in cross coupling reactions. Previous attempts to effect cross coupling of aryl $OPO(NEt_2)_2$ under Kumda type conditions by Alessi[19] had proved unsuccessful (Table. 4.1).

Table 4.1 Attempted Kumada- Corriu Cross Coupling Reactions of Aryl Phosphorodiamidates.



4.5 **4.6**

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
IPrNi(Cp)Cl	2-MeC_6H_4MgCl	Et_2O / rt / 15h
IMesNi(Cp)Cl	$TMSCH_2MgCl$	Et_2O / rt / 15h

Successful cross coupling of aryl $OPO(NEt_2)_2$ systems with organoboranes would dramatically increase the synthetic utility of this new DMG. In 2007 prior to the publications of Chatani,[14] Garg[17] and Shi[16], the precedents of Kumada,[20] Stille,[21] Suzuki,[22] and Negishi[23,22c] cross coupling reactions of vinylphosphates offered hope for the establishment of the aryl $OPO(NEt_2)_2$ cross coupling reaction.

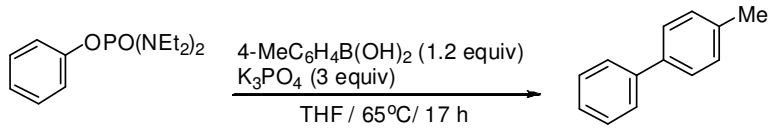
4.4 Results and Discussion

4.4.1 Cross Coupling Aryl $OPO(NEt_2)_2$ Derivatives

Initial attempts were carried out in collaboration with Frendo-Cumbo.[24] It was only according to the conditions established by Skrydstrup[25] for the coupling of

vinylphosphates with arylboronic acids that low yields of products were observed (Entry 4, Table 4.2).

Table 4.2. Initial catalyst screening for the Cross coupling of Aryl $OPO(NEt_2)_2$ Derivatives with p-Tolyl boronic acid.



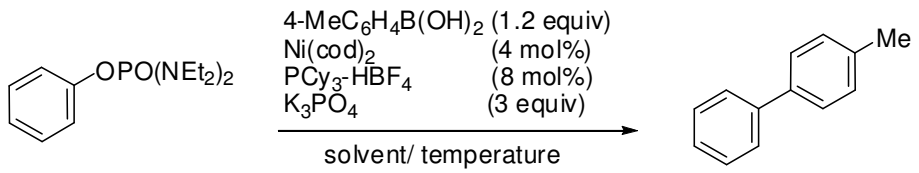
4.7 **4.8**

Entry	Catalyst (5 mol%)	Ligand (mol%)	Yield % (GC/MS)
1	$NiCl_2$	dppf (8 mol%)	---
2	$Ni(COD)_2$	P^tBu3 (6 mol%)	trace
3	$Pd(dba)_2$	PCy_3HBF_4 (8 mol%)	---
4	$Ni(COD)_2$ (4%)	PCy_3HBF_4 (8 mol%)	17%
5	Ni(acac)2 (4%)	PCy_3HBF_4 (8 mol%)	---
6	IMesNi(Cp)Cl, IPrNi(Cp)Cl, SiMesNi(Cp)Cl	---	---

Interestingly the $OPO(NEt_2)_2$ group was found to be inert to cross coupling under palladium catalysis, a fact which has implications for the development of orthogonal cross coupling partners. In examination of ligands with various Ni^0 sources, tricyclohexyl phosphine was found to be the only successful catalytic system, with the highly active tri-*tert*-butyl phosphine and various N-heterocyclic carbene ligands ineffective.

Further optimization proved to be difficult with solvent and temperature playing a significant role. Switching to a non-coordinating high boiling solvent such as toluene resulted in an impressive increase in the yield.

Table 4.3 Solvent Screen for the Cross Coupling of Phenyl *O*PAm 4.7.



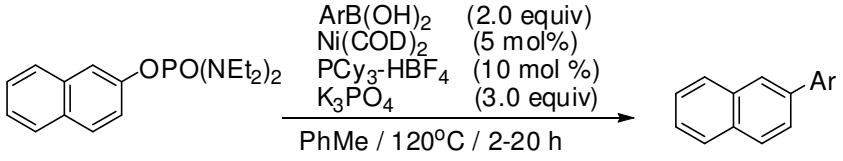
4.7 **4.8**

Entry	Solvent / temperature	Yield GC/MS
1	DMF / reflux / 24h	---
2	dioxane / reflux / 24h	---
3	DME / reflux / 24h	---
4	toluene / reflux / 24h	44%

Although numerous further attempts to optimize were unsuccessful a number of issues were recognized: 1) Reaction proved to be poorly reproducible, 2) $Ni(cod)_2$ was found to be unstable and difficult to maintain outside of the glove box, 3) K_3PO_4 was the only functional base and required scrupulously drying before use. Although our experience was frustrating, the work of Chatani[14] in early 2008 was heartening since it confirmed the extreme specificity of this catalytic system.

The 2-napthyl *O*PAm derivative **4.9** was chosen for exploration because of its increased reactivity and the ability to track its reduction product via GC/MS to help optimization of the reaction. The loading of the boronic acid was increased to two equivalents in addition to a small increase in catalyst and ligand, 5% and 10%

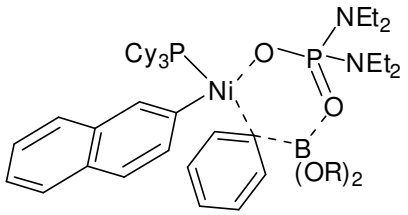
respectively. A variety of boronic acids were demonstrated to cross couple in good to excellent yield making an excellent starting point to the development of a new Suzuki-Miyaura methodology (Scheme 4.2). The analogous transmetalation intermediate of Shi[16] is tentatively proposed for this reaction.



4.9 **4.10a-f**

4.10a-f	Ar	Yld %
a	C_6H_5	96
b	C_6H_5-2-Me	72
c	C_6H_5-4-Me	89
d	C_6H_5-2-F	63
e	C_6H_5-4-CF_3	79
f	C_6H_5-4-F	68

Proposed Transmetalation Intermediate



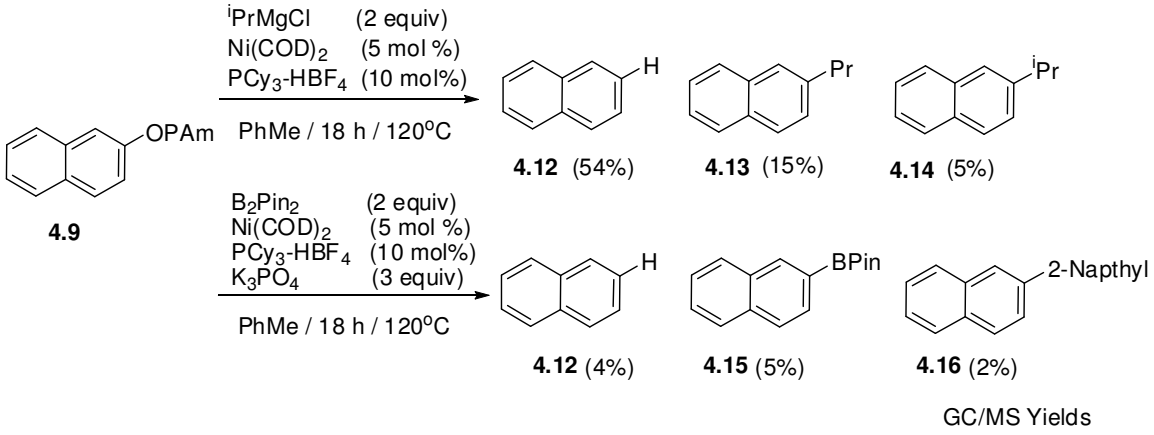
4.11

Scheme 4.2 Cross Coupling of Aryl *O*-Phosphorodiamidates 4.9 with Aryl Boronic Acids.

Significant problems with the instability of $Ni(COD)_2$ were encountered and although precautions were taken, best results were obtained with catalyst used within 3 days after removal from the glove box. In addition boronic acids recrystallized from hexanes or hexanes/ethyl acetate appeared to give much better results, observations which foreshadow results later obtained in the cross coupling of the *N-N*-diethylcarbamate (Section 4.4.2).

In addition to efforts in the above cross coupling chemistry, the reductive cleavage of the $OPO(NEt_2)_2$ group with a good beta-hydride donor $^{i}PrMgCl$ was

undertaken. Initial results showed that the $OPO(NEt_2)_2$ could be cleaved reductively from 2-napthyl *O*PAm **4.9** although additional products **4.13** and **4.14** provided evidence for the isomerized alkyl coupling in low yield. In addition borylation of **4.9** using B_2Pin_2 led to the formation of the desired product **4.15** albeit in very low yield along with similar yields of the homo coupled product **4.16,** expected under these conditions, and the de-OPAm product **4.12**.



Scheme 4.3. Reductive dephosphanoamidoylation and Borylation of 2-Naphhtyl OPO(NEt2)2 4.9.

4.4.2 Cross coupling of Aryl $OCONEt_2$ Derivatives

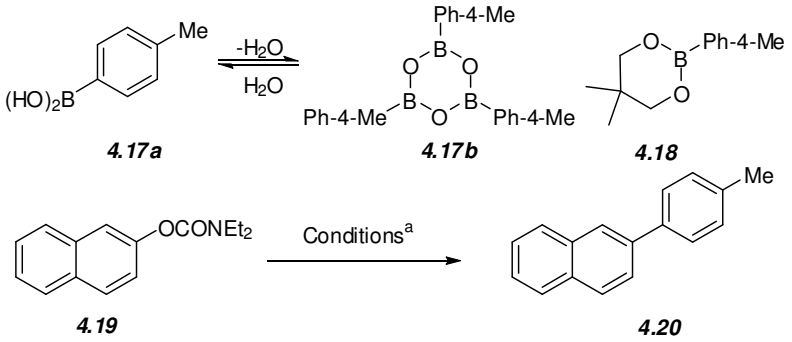
The powerful N,N-diethyl *O*-carbamate DMG[26] and its considerable utility in synthetic aromatic chemistry which has been extensively applied in the last 25 years[27,28] has stimulated our continuing efforts to increase its cross coupling potential. The work described in this section was carried out in collaboration with Antoft-Finch.[29]

Scouting cross coupling investigations on 2-naphthyl *O*-carbamate **2** with *para*-tolylboronic acid (PTBA) were carried out partially based on results observed with the

$OPO(NEt_2)_2$ group (Section 4.4.1) and those of Garg,[17] Selected examples are collected in (Table 4.4). Although producing similar results, the more stable $NiCl_2(PCy_3)_2$ was used rather than $Ni(cod)_2$ due to inconsistency of observed results (compare entries 8 and 9). The detrimental effect of the hydroscopic base necessitated the use of scrupulously dried material (entry 4). Other potentially critical factors investigated were the presence of NiO[30] (derived from $Ni(cod)_2$ oxidation), traces of Pd[31] (entry 3). It was only after observing a significant difference in reactivity using various samples of both commercial and prepared PTBA under identical experimental conditions that the culprit parameters were revealed.

After extensive ^1H and ^{11}B NMR spectroscopic studies, it was established that a) under strictly anhydrous conditions, the boroxine **1b** is inefficient in the coupling reaction (entry 7); b) PTBA (**1a**) liberates excessive water in organic solvents which is detrimental to the reaction (entry 6); c) the ratio of **1b**:**1a** = 10:1 is most effective for the reaction. Since addition of water to the boroxine is inaccurate on small scale, the boronic acid was dried to various degrees in order to control the relative amount of contained water. With this information in hand, optimization led to full conversion within 5 h using only 5 mol% of catalyst (entry 11).

Table 4.4. Optimization of Conditions for the Cross Coupling of 4.19 with 4.20.



#	Solvent	°C	Catalyst (5 mol%)	Ligand (mol%)[b]	K_3PO_4 (equiv)	$ArB(OR)_2$ (equiv)[c]	Yield (%)[d]
1	Dioxane	120	$Ni(cod)_2$	10	3	***4.17b/a*** (2.0)	0
2	PhMe	120	NiO	10	3	***4.17b/a*** (2.0)	0
3	PhMe	120	$Ni(cod)_2$	10	3	***4.18*** (2.5)	0
4	PhMe	120	$Ni(cod)_2$[e]	10	5	***4.17b/a*** (2.5)	11
5	PhMe	120	$NiCl_2(PCy_3)_2$	10	3[g]	***4.17b/a*** (2.0)	37
6	*o*-xylene	150	$NiCl_2(PCy_3)_2$	10	5	***4.17b/a***[h] (2.5)	26
7[f]	*o*-xylene	150	$NiCl_2(PCy_3)_2$	10	5	***4.17b*** (2.5)	61
8	PhMe	120	$Ni(cod)_2$	10	5	***4.17b/a*** (2.5)	69
9	PhMe	120	$NiCl_2(PCy_3)_2$[i]	-	7.2	***4.17b/a*** (4.0)	69
11[f]	*o*-xylene	150	$NiCl_2(PCy_3)_2$	10	5	***4.17b/a*** (2.5)	100/ (84)[j]

[a] Reaction was quenched after 20 h. [b] Ligand= PCy_3HBF_4. [c] Equivalents based on [$ArB(OR)_2$], ratio of ***1b***:***1a*** 10:1. [d] Yield based on GC/MS analysis. [e] Added 1 mol% $PdCl_2$ to reaction. [f] Reaction was quenched after 5 hours. [g] Hydrate was used. [h] ratio of ***1b***:***1a*** 1:1. [i] 10 mol% used. [j] Isolated yield.

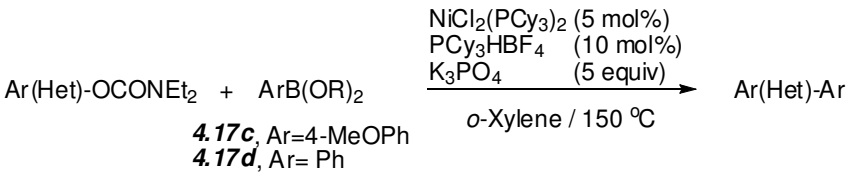
As with related coupling reactions of organoboron compounds, the control of the hydrolysis equilibrium between free boronic acid and the less reactive boroxine is

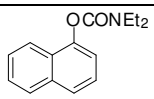
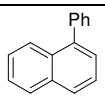
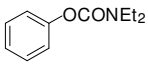
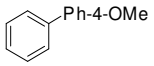
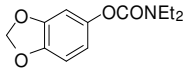
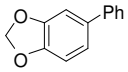
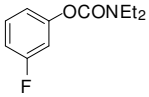
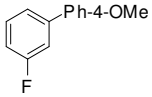
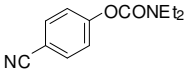
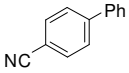
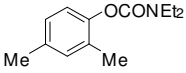
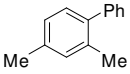
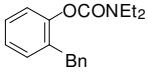
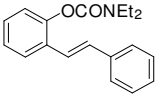
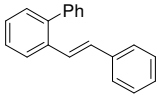
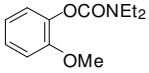
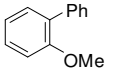
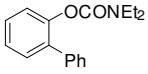
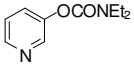
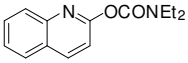
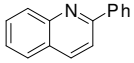
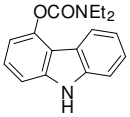
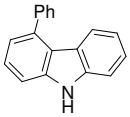
important to the success of the reaction.[32] The role of water was found to be critical by Shi[16] for aryl acetate derivatives. In the case of the corresponding diethyl *O*-carbamate, problems were not expected to its hydrolytic stability. 2-Naphthol or any other hydrolysis product were not isolated or detected by GC/MS analysis under these conditions.[27]

Detailed studies performed by Liu[33] suggest the intermediacy of a monophosphine Ni^0 pathway for the oxidative addition and transmetalation with $K[PhB(OH)_3]$. We speculate that very little water is necessary to generate the quaternized boron "ate" complex, however any excess water significantly hinders catalytic activity by the formation of inactive nickel hydroxides/oxides.[34]

Our attention turned to define the scope and tolerance of the aryl OAm cross coupling transformation (Table 2). Simple and fused aromatic substrates underwent smooth cross coupling. In comparison, the presence of a EWG substituent (entry 4) showed a higher reactivity while an EDG-containing substrate (entry 3) gave poor yields of product. A cyano derivative (entry 5) appeared aberrant leading to low yields of product as a result of to cross coupling at the cyano group resulting in a mixture of products. Shi reported this same transformation, during the course of this work.[35] In some cases, steric hindrance was found to be detrimental for this transformation (entry 6), however various *ortho* substituted derivatives (methoxy, benzyl, styryl, and phenyl) proceeded to give expected products in good to excellent yields (entries 7-10).

Table 4.5. Suzuki-Miyaura Cross Coupling of Aryl *O*-carbamates.



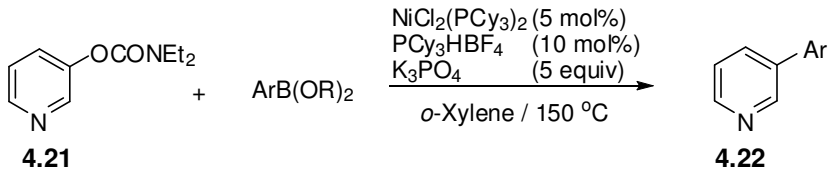
Entry	Ar(Het)-OCONEt$_2$	ArB(OR)$_2$[a]	Product	Yield[b]	Yield[c]
1		***4.17d***		100%	82%
2		***4.17c***		64%	58%
3		***4.17d***		23%	31%
4		***4.17c***		80%	69%
5		***4.17d***		36%	28%
6		***4.17d***		8%	-
7		***4.17d***		60%	70%
8		***4.17d***		99%	93%
9		***4.17d***		40%	36%
10		***4.17d***		69%	50%
11		***4.17d***		100%	85%
12		***4.17d***		100%	51%
13		***4.17d***		45%	55%

[a] ArB(OR)$_2$ (2.5 equiv), ratio of $Ar_3B_3O_3$: ArB(OH)$_2$ 10:1. [b] GC/MS yields. [c] Isolated yields.

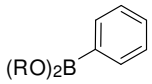
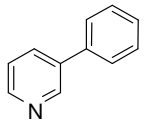
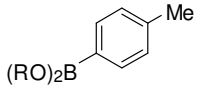
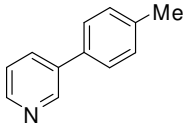
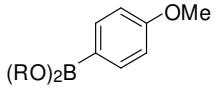
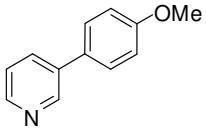
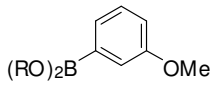
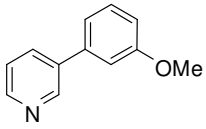
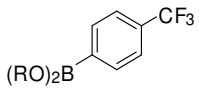
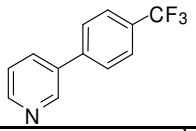
It is only under these optimized conditions that *ortho* substituted *O*-carbamates can be cross coupled efficiently; using previously cited conditions[17] (Table 4.5, entry 7), no cross coupling or very poor yields of products were obtained. Inclusion of heterocycles into this methodology was possible and the synthesis of pyridyl, quinolyl, and carbazole aryl derivatives was achieved in good yields (Table 4.5, entries 11-13).

Due to its high reactivity and ease of purification, the 3-pyridyl O-carbamate **4.21** was chosen as the test substrate for coupling with a variety of boroxines (Table 4.6).

Table 4.6. Cross Coupling of 3-pyridyl *O*-carbamate 4.21 with Aryl Boroxines.



4.21 **4.22**

Entry	$ArB(OR)_2$[a]	Product	Yield[b]
1			85%
2			87%
3			84%
4			65%
5			70%

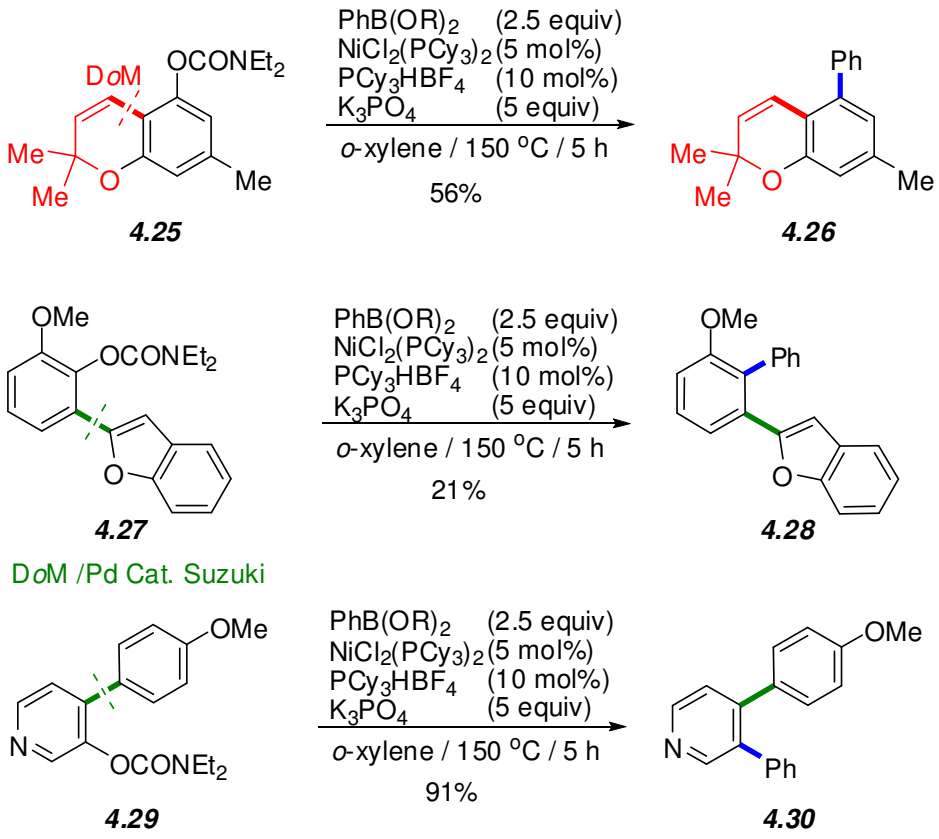
[a] $[ArB(OR)_2]$ (2.5 equiv) , ratio of $Ar_3B_3O_3$: $ArB(OH)_2$ 10:1. [b] Isolated yields.

As gleaned from Table 4.6, electron rich examples, (entries 1-3) provided the desired products in good yields while electron deficient derivatives (entries 4-5) provide the products in lower yields.

As a demonstration of the enhanced synthetic utility of the diethyl *O*-carbamate cross coupling reaction, the synthesis of three new compounds either difficult or impossible to prepare by classical methods was undertaken (Scheme 4.4). The *2H*-chromene **4.26** was readily available in a one step D*o*M reaction – senecioaldehyde quench and subsequent O-to-O carbamoyl transfer and acid-catalyzed cyclization to give **4.25** in 54% yield.[36] Compound **4.25** was exploited in the total synthesis of plicadin,[37] The Ni catalyzed cross coupling of **4.25** with phenyl boroxine gave the 5-phenyl- *2H*-chromene **4.26** in 56% yield. Uniquely substituted 5-phenyl-*2H*-chromene, represent a heterocyclic framework of bioactivity[38] and natural product interest.[39]

D*o*M chemistry also allows the regioselective construction of *ortho* boron or halo substituted cross coupling partners which may be subsequently used in palladium catalyzed cross couplings reactions. Two examples of heterobiaryls prepared previously by this strategy are **4.27**[40] and **4.29**.[41] In view of the unreactivity of the *O*-carbamate palladium catalyzed cross coupling, it assumes an orthogonal cross coupling partner role when fused with the nickel coupling strategy. This is demonstrated in the synthesis of **4.28** and **4.30**. There exists few methods to obtain the *1,2,3*- substitution pattern of heteroarane **4.28.** Interestingly, the low yield of product **4.28** is a result of reductive cleavage and arylation of benzofuran rather than low reactivity of starting **4.27** due to steric hindrance effects.

Only two methods exist for synthesis of non identical 3,4-diaryl pyridines of the **4.30** type.[42] The present method offers a new straight forward entry into this class of compounds with potential for generalization.



Scheme 4.4 Cross coupling of N,N-diethyl aryl *O*-carbamates 4.26-4.28 with Phenyl Boroxines.

4.5 Conclusions

The synthetic utility of the $OPO(NEt_2)_2$ (OPAm) DMG has been enhanced by the discovery and optimization of a new nickel catalyzed cross coupling of aryl OPAm derivatives. The derived conditions were applied to the analogous N,N-diethyl *O*-carbamate (OAm) DMG which has a long history of synthetic utility. Initially results from attempts to effect a Suzuki-Miyaura aryl OAm cross coupling reaction under Ni-catalyzed conditions gave very poor results. This was very fruitful as insights into the catalytic system and crucial role of water were gained. Optimized conditions for the aryl OAm –boroxine coupling reaction were found using the inexpensive and bench stable $NiCl_2(PCy_3)_2$ catalyst precursor which then allowed the generalization of the reaction using many aryl OAm derivatives, including *ortho* substituted substrates.

This methodology demonstrates another important connection to directed *ortho* metalation (DoM) chemistry and enhances the synthetic versatility of the *O*-carbamate, as demonstrated by the rapid synthesis of new heterocyclic compounds **4.26**, **4.28**, and **4.30**.

Although the established conditions (see Scheme 4.2) to effect the cross coupling of aryl the $OPO(NEt_2)_2$ appear adequate, given the diminished OPAm C_{aryl}-O bond strength and increased coordinated ability, it is anticipated that extremely efficient cross coupling reactivity of these derivatives will be uncovered by application of the new reoptimized conditions used for the OAm coupling reactions.

Experimental Section for Chapter 4

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 prepared by evaporation of CH_2Cl_2 solutions or as KBr pellets using a BONEM FT-IR spectrophotomer. NMR spectra were recorded on a Bruker Avance-300, 400 or 500 MHz. GC/MS 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. Anhydrous toluene were obtained by forced passage through activated alumina in a Pure-Solv 400 solvent purification system (Innovative Technology, Inc.) whereas the anhydrous xylenes mixture was purchased from Sigma-Aldrich Chemical Co. Where appropriate, reactions were monitored by TLC and GC/MS. Flash column chromatography was carried out using Silicycle Silia-P Flash Silica Gel. K_3PO_4 was dried by heating at 250^oC under vacuum for 5 h and stored in sealed vials under nitrogen.

General Procedure A: Cross Coupling of $OCONEt_2$ or $OPO(NEt_2)_2$

A 5 mL flame dried vial containing aTeflon coated stir bar was cooled to rt under nitrogen and capped. Reagents and reactants were weighed and added under an atmosphere of nitrogen. Solvents, stored in a Schlenk flask, were then added via septum cap syringe injection under nitrogen. The vial was then capped and stirred at rt for a short

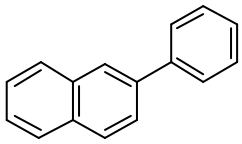
period of time (1 min) to ensure complete dissolution of catalyst. The solution was stirred at the indicated temperatures and the reaction was monitored periodically by GC/MS and TLC at the following time intervals: 0.5 h, 1h, 2 h, 5 h. The reaction was stopped when total disappearance of the starting material or no further conversion to the product was observed. The mixture was then cooled to rt and concentrated, Deionized H_2O (1 mL) was added to the residue and the mixture was extracted with EtOAc (4 X 1.5 mL). The combined organic fractions were dried (Na_2SO_4), subjected to filtration, and concentrated to dryness under reduced pressure. The residue was dissolved in a minimum amount of CH_2Cl_2 and purified by silica gel flash column chromatography column using the specified eluent to afford the product.

General Procedure B: Dehydration of Boronic Acids

Boroxines were prepared from commercial or prepared boronic acids by heating at 60-80^{o}C under vacuum for 6-8 h using a Kugelrohr apparatus. Prior to use of the boroxine, its ^{1}H NMR spectrum was recorded to determine the ratio of boroxine: water content. If the ratio was within the range of 1:0.08-1:0.11 (boroxine: water), and 1:0.06-1:0.1 (boroxine: boronic acid), then the boronic anhydride was deemed suitable for undertaking the cross-coupling reaction.

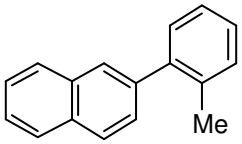
Cross Coupling of the $OPO(NEt_2)_2$ Group

2-phenylnaphthalene **4.10a**



Preparation of this compound was carried out in accordance with **General Procedure A** using the following materials: $Ni(cod)_2$ (4 mg, 0.015 mmol), anhydrous K_3PO_4 (190 mg, 0.9 mmol), phenyl boronic acid (73 mg, 0.6 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), 2-naphthyl tetraethylphosphorodiamidate (100 mg, 0.3 mmol) added in PhMe (1.5 mL, 0.2M). The reaction was stirred at 120 ^oC, until complete disappearance of the starting material was observed by GC/MS (20h). Standard workup and flash silica gel chromatogrpahy, isocratic elution in hexanes to afford the product (96%, 59 mg, 0.29 mmol) as a colorless solid. ^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.07 (s, 1H), 8.00- 7.87(m, 3H), 7.79 -7.74 (m, 3H), 7.56-7.48 (m, 3H), 7.40 (t, *J* = 7.3 Hz, 1H). The spectral properties were shown to be identical to those reported.[14]

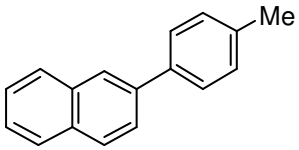
2-o-tolylnaphthalene **4.10b**



Preparation of this compound in accordance with **General Procedure A** using the following materials: $Ni(cod)_2$ (4 mg, 0.015 mmol), anhydrous K_3PO_4 (190 mg, 0.9 mmol), *o*-toyl boronic acid (81 mg, 0.6 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), 2-naphthyl tetraethylphosphorodiamidate (100 mg, 0.3 mmol) added in PhMe (1.5 mL, 0.2M). The

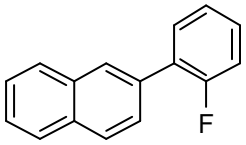
reaction was stirred at 120 °C, after 20 hours no further conversion to the product (67%) was observed by GC/MS. Purification of the crude by column chromatography, silica gel, gradient elution in hexanes to 5:1 (hexanes: ethyl acetate) over 200 mL to afford the product (72%, 47 mg, 0.22 mmol) as a colorless solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.99-7.94 (m, 2H), 7.89 (s, 1H), 7.62-7.58 (m, 3H), 7.45-7.41 (m, 4H), 2.43 (s, 3H). Matching the reported spectra.[14]

2-*p*-Tolylnaphthalene **4.10c**



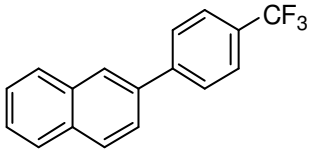
Preparation of this compound in accordance with **General Procedure A** using the following materials: Ni(cod)$_2$ (4 mg, 0.015 mmol), anhydrous K_3PO_4 (190 mg, 0.9 mmol), *p*-toyl boronic acid (81 mg, 0.6 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), 2-naphthyl tetraethylphosphorodiamidate (100 mg, 0.3 mmol) added in PhMe (1.5 mL, 0.2M). The reaction was stirred at 120 °C, after 2 hours complete disappearance of the starting material was observed by GC/MS. Purification of the crude by column chromatography, silica gel, gradient elution in hexanes to 5:1 (hexanes: ethyl acetate) over 200 mL to afford the product (89%, 58 mg, 0.27 mmol) as a colorless solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.03 (s, 1H), 7.94-7.83 (m, 3H), 7.74 (dd, J = 8.50, 1.09 Hz, 1H), 7.63 (d, J = 7.94 Hz, 2H), 7.54-7.43 (m, 2H), 7.37-7.27 (m, 2H), 2.41 (s, 3H). Spectra match those previously reported.[43]

2-(2-fluorophenyl)naphthalene **4.10d**



Preparation of this compound in accordance with **General Procedure A** using the following materials: $Ni(cod)_2$ (4 mg, 0.015 mmol), anhydrous K_3PO_4 (190 mg, 0.9 mmol), *2*-fluoro boronic acid (83 mg, 0.6 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), 2-naphthyl tetraethylphosphorodiamidate (100 mg, 0.3 mmol) added in PhMe (1.5 mL, 02M). The reaction was stirred at 120 ^oC, , after 20 hours no further conversion to the product (68%) was observed by GC/MS. Purification of the crude by column chromatography, silica gel, gradient elution in hexanes to 5:1 (hexanes: ethyl acetate) over 200 mL to afford the product 63%, 42 mg, 0.19 mmol) as a light yellow oil. ^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.04 (s, 1H), 7.95-7.85 (m, 3H), 7.71 (d, J = 8.6 Hz, 1H), 7.60-7.18 (m, 6H), Matching the reported spectra.[14]

2-(4-(trifluoromethyl)phenyl)naphthalene**4.10e**

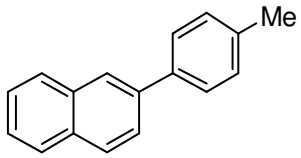


Preparation of this compound in accordance with **General Procedure A** using the following materials: $Ni(cod)_2$ (4 mg, 0.015 mmol), anhydrous K_3PO_4 (190 mg, 0.9 mmol), 4-(trifluoromethyl)phenyl boronic acid (113 mg, 0.6 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), 2-naphthyl tetraethylphosphorodiamidate (100 mg, 0.3 mmol) added in PhMe (1.5 mL, 0.3M). The reaction was stirred at 120 ^oC, after 20 hours , after 20 hours no further conversion to the product (72%) was observed by GC/MS. Purification of the crude by column chromatography, silica gel, gradient elution in hexanes to 5:1 (hexanes:

ethyl acetate) over 200 mL to afford the product 68%, 42 mg, 0.2 mmol) as a colorless solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.07 (s, 1H), 7.97-7.81 (m, 5H), 7.76-7.72 (m, 3H), 7.55-7.52 (m, 2H), Matching the reported spectra.[14]

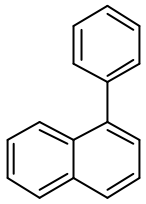
Cross Coupling of the OCONEt$_2$ Group

4-*p*-tolylnaphthalene (**Table 4.4, entry 11**)



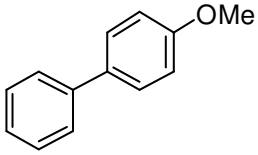
Preparation of this compound in accordance with **General Procedure A** using the following materials: 2-naphthyl diethylcarbamate (73 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), tri(*p*-tolyl) boroxine (101 mg, 0.32 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^{o}C, after 5 hours complete disappearance of the starting material was observed by GC/MS. Purification of the crude was performed using preparatory TLC developed in hexanes to afford the product (84%, 54.8 mg, 0.25 mmol) as a colorless solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.03 (s, 1H), 7.94-7.83 (m, 3H), 7.74 (dd, J = 8.50, 1.09 Hz, 1H), 7.63 (d, J = 7.94 Hz, 2H), 7.54-7.43 (m, 2H), 7.37-7.27 (m, 2H), 2.41 (d, J = 14.66 Hz, 3H). Spectra match those previously reported.[43]

1-phenylnaphthalene (**Table 4.5, entry 1)**



Preparation of this compound in accordance with **General Procedure A** using the following materials: 1-naphthyl diethylcarbamate (73 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), triphenyl boroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours complete disappearance of the starting material was observed by GC/MS. Purification of the crude was performed using preparatory TLC developed in hexanes to afford the product (82%,50 mg, 0.24 mmol) as a colorless solid. ^1H NMR (400 MHz, *CDCl₃*) δ ppm 7.91 (d, *J* = 8.40 Hz, 2H), 7.89-7.85 (m, 1H), 7.55 (d, *J* = 7.08 Hz, 1H), 7.47-7.41 (m, 3H), 7.51 (d, *J* = 2.26 Hz, 2H), 7.50 (d, *J* = 1.12 Hz, 2H), 7.49-7.47 (m, 1H). Spectra match those previously reported.[44]

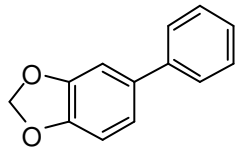
4-methoxybiphenyl (**Table 4.5, entry 2)**



Preparation of this compound in accordance with **General Procedure A** using the following materials: phenyl diethylcarbamate (59 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5mmol), tris(*p*-Methoxyphenyl) boroxine (116 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours no further conversion to the product (64%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, isocratic elution with hexanes to afford the product in (58%, 32 mg, 0.17 mmol)

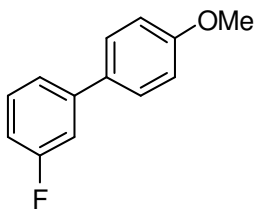
as a colorless solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm, 7.60-7.50 (m, 4H), 7.42 (t, *J* = 7.65, 7.65 Hz, 2H), 7.31 (t, *J* = 7.35, 7.35 Hz, 1H), 7.01-6.95 (m, 2H), 3.86 (s, 3H). Spectra match those previously reported.[45]

5-phenylbenzo[d][1,3]dioxole (**Table 4.5, entry 3)**



Preparation of this compound in accordance with **General Procedure A** using the following materials: benzo[d][1,3]dioxol-5-yl diethylcarbamate (71 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5mmol), triphenyl boroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^{o}C, after 5 hours no further conversion to the product (23%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, isocratic elution with hexanes to afford the product (31%, 19 mg, 0.095 mmol) as a light yellow oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.53 (d, *J* = 7.32 Hz, 2H), 7.42 (t, *J* = 7.52, 7.52 Hz, 2H), 7.32 (t, *J* = 7.28, 7.28 Hz, 1H), 7.08 (d, *J* = 8.54 Hz, 2H), 6.90 (d, *J* = 7.82 Hz, 1H), 6.01 (s, 2H). Spectra match those previously reported.[46]

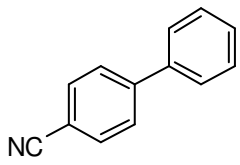
3-fluoro-4'-methoxybiphenyl (**Table 4.5, entry 4**)



Preparation of this compound in accordance with **General Procedure A** using the following materials: 3-flourophenyl diethylcarbamate (66 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5mmol), tris(*p*-Methoxyphenyl) boroxine (116 mg,

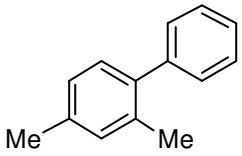
0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours no further conversion to the product (80%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, isocratic elution in isocratic hexanes. Further purification was performed using preparatory TLC developed in 7:1 (hexanes/CH_2Cl_2) to afford the product (69%, 42 mg, 0.21 mmol) as colorless crystals. ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.46 (d, *J* = 8.66 Hz, 2H), 7.36-7.27 (m, 2H), 7.19 (d, *J* = 10.92 Hz, 1H), 6.99-6.89 (m, 3H), 3.83-3.77 (m, 3H). Spectra match those previously reported.[47]

biphenyl-4-carbonitrile (**Table 4.5, entry 5**)



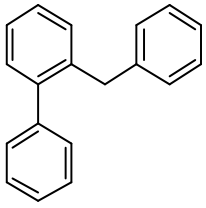
Preparation of this compound in accordance with **General Procedure A** using the following materials: 4-cyanophenyl diethylcarbamate (65 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$, (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), triphenyl boroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150^oC, after 5 hours no further conversion to the product (36%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, isocratic elution with hexanes to afford the product (28%, 15 mg, 0.08 mmol) as a light orange oil. ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.70 (td, *J* = 16.83, 8.33, 8.33 Hz, 4H), 7.59 (d, *J* = 7.05 Hz, 2H), 7.49 (t, *J* = 7.29, 7.29 Hz, 2H), 7.43 (d, *J* = 7.21 Hz, 1H). Spectra match those previously reported.[48]

2,4-dimethylbiphenyl **(Table 2, entry 6)**



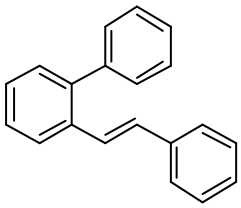
Preparation of this compound in accordance with **General Procedure A** using the following materials: 4-cyanophenyl diethylcarbamate (65 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$, (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), triphenyl boroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150^{o}C, after 20 hours no further conversion to the product (8%) was observed by GC/MS. Isolation was not attempted. LRMS (EI) (*m/z)* (%) 182[M^+] (70), 167(100), 51(60), 62(55), 77(50), 115(48), 152(45). Mass spectra match those previously reported.[49]

2-benzylbiphenyl (**Table 2, entry 7**)



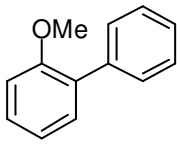
Preparation of this compound in accordance with **General Procedure A** using the following materials: 2-benzylphenyl diethylcarbamate (85 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), triphenylboroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^{o}C, after 5 hours no further conversion to the product (60%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, isocratic elution with hexanes to afford the product (70%, 52 mg, 0.21 mmol) as a light brown oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.59 (d, *J* = 8.07 Hz, 1H), 7.43 (dd, *J* = 13.65, 6.57 Hz, 1H), 7.34 (t, *J* = 8.45, 8.45 Hz, 4H), 7.25-7.06 (m, 7H), 6.97 (d, *J* = 7.31 Hz, 1H), 3.97 (d, *J* = 12.11 Hz, 2H). Spectra match those previously reported.[50]

(E)-2-styrylbipheny (**Table 4.5, entry 8**)



Preparation of this compound in accordance with **General Procedure A** using the following materials: (*E*)-2-styrylphenyl diethylcarbamate (58 mg, 0.184 mmol), $NiCl_2(PCy_3)_2$ (6.3 mg, 0.0091 mmol), anhydrous K_3PO_4 (194 mg, 0.914 mmol), triphenyl boroxine (55 mg, 0.175 mmol), PCy_3HBF_4 (6.7 mg, 0.0183 mmol) *o*-xylene (0.75 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours no further conversion to the product (99%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, isocratic elution with hexanes to afford the product (93%, 44 mg, 0.17 mmol) as a light yellow oil. ^1H NMR (400 MHz, *CDCl₃*) δ ppm 7.68 (d, J = 7.48 Hz, 1H), 7.36 (t, J = 4.21, 4.21 Hz, 1H), 7.34 (d, J = 2.97 Hz, 2H), 7.31 (d, J = 6.46 Hz, 3H), 7.29-7.26 (m, 3H), 7.22 (t, J = 7.51, 7.51 Hz, 2H), 7.19-7.11 (m, 2H), 7.09-7.01 (m, 1H), 7.01-6.93 (m, 1H). Spectra match those previously reported.[51]

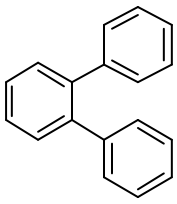
2-methoxybiphenyl (**Table 4.5, entry 9**)



Preparation of this compound in accordance with **General Procedure A** using the following materials: 2-methoxyphenyl diethylcarbamate (63 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), triphenyl boroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours no further conversion to the product (40%) was observed by

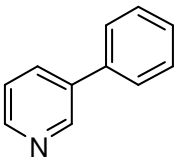
GC/MS. Purification of the crude was performed using flash chromatography, silica column, isocratic elution in 5:1 (hexanes/ ethyl acetate) to afford the product (36%, 20 mg, 0.11 mmol) as a light green/yellow oil. ^{1}H NMR (400 MHz, *$CDCl_3$)* δ ppm 7.59 (d, J=7.2 Hz, 2 H), 7.45 (t, J=7.3 Hz, 2 H), 7.32–7.41 (m, 3H), 7.07 (t, J=7.4 Hz, 1H), 7.02 (d, J=8.0 Hz, 1H), 3.88 ppm(s, 3 H). Spectra match those previously reported.[52]

o-terphenyl (**Table 4.5, entry 10**).



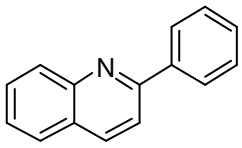
Preparation of this compound in accordance with **General Procedure A** using the following materials: 2-biphenyl diethylcarbamate (43 mg, 0.16 mmol), $NiCl_2(PCy_3)_2$ (5.5 mg, 0.008 mmol), anhydrous K_3PO_4 (170 mg, 8 mmol), triphenyl boroxine (48 mg, 0.153 mmol), PCy_3HBF_4 (5.9 mg, 0.016 mmol), *o*-xylene (0.8 mL, 0.2M). The reaction was stirred at 150 ^{o}C, after 5 hours no further conversion to the product (69%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, isocratic elution in hexanes with the addition of 2% ethyl acetate. Further purification by Prep TLC was performed using isocratic hexanes with the addition of 2% ethyl acetate to afford the product (50%, 18.3 mg, 0.08 mmol) as a clear oil. ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.37-7.31 (m, 4H), 7.17-7.09 (m, 6H), 7.09-7.02 (m, 4H). Spectra match those previously reported.[45]

3-phenylpyridine (**Table 4.5, entry 10**).



Preparation of this compound in accordance with **General Procedure A** using the following materials: 3-pyridinyl diethylcarbamate (58 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), triphenylboroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours complete disappearance of the starting material was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, using a gradient elution of 1:1 to 1:3 (hexanes/ ethyl acetate+ 2% NEt_3) over 200 mL to afford the product isolated (85%, 40 mg, 0.26 mmol) as a light yellow oil. ^1H NMR (400 MHz, *CDCl₃*) δ ppm 8.85 (s, 1H), 8.59 (d, *J* = 4.67 Hz, 1H), 7.88 (d, *J* = 7.82 Hz, 1H), 7.59 (d, *J* = 8.16 Hz, 2H), 7.48 (t, *J* = 7.59, 7.59 Hz, 2H), 7.44-7.40 (m, 1H), 7.37 (dd, *J* = 7.80, 4.88 Hz, 1H). Spectra match those previously reported.[53]

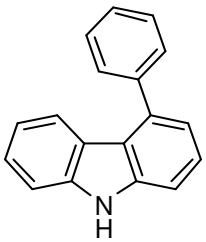
2-phenylquinoline (**Table 4.5, entry 11**).



Preparation of this compound in accordance with **General Procedure A** using the following materials: 2-quinolinyl diethylcarbamate (72 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5mmol), triphenylboroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours complete disappearance of the starting material was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica

column, isocratic elution 5:1: (Hexanes: Ethyl Acetate + 2% NEt_3) to afford the product (51%, 31 mg, 0.15 mmol) as light yellow solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.23 (d, *J* = 8.53 Hz, 1H), 8.17 (d, *J* = 6.31 Hz, 2H), 7.89 (d, *J* = 8.57 Hz, 1H), 7.84 (d, *J* = 8.16 Hz, 1H), 7.74 (t, *J* = 7.67, 7.67 Hz, 1H), 7.60 (d, *J* = 7.36 Hz, 1H), 7.54 (t, *J* = 7.23, 7.23 Hz, 2H), 7.46 (dd, *J* = 16.64, 7.55 Hz, 2H). Spectra match those previously reported.[53]

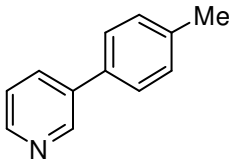
4-phenyl-9H-carbazole (**Table 4.5, entry 12**).



Preparation of this compound in accordance with **General Procedure A** using the following materials: 9H-carbazol-4-yl diethylcarbamate (85. mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), triphenyl boroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^{o}C, after 5 hours no further conversion to the product (45%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, eluted with hexanes to afford the product (55%, 40 mg, 0.165 mmol) as transparent, light yellow oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.02 (dd, *J* = 7.14, 1.00 Hz, 1H), 7.36-7.31 (m, 1H), 7.40 (ddd, *J* = 14.67, 7.39, 2.14 Hz, 3H), 7.46-7.44 (m, 1H), 7.57-7.52 (m, 1H), 7.26-7.22 (m, 1H), 7.14 (ddd, *J* = 8.01, 5.87, 1.91 Hz, 1H), 7.99 (d, *J* = 7.80 Hz, 1H), 6.92-6.85 (m, 1H), 7.30 (s, 1H), 8.13 (d, *J* = 12.27 Hz, 1H); ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 109.5 (1C), 110.4 (1C), 118.9 (1C), 119.3 (1C), 120.2 (1C), 122.4 (1C), 125.8 (1C), 137.5 (1C), 127.4 (1C), 129.2 (2C), 128 (2C), 139.7 (1C), 121.0

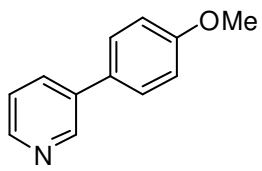
(1C), 125.5 (2C), 110.6 (1C); IR (film CH_2Cl_2) V_{max} cm^{-1} 3415, 2928, 1602, 1456, 1386, 1334, 1323, 757, 728, 701. LRES MS (EI) *m/z* (%) 243[M^+](100), 242 (51), 68 (52), 241 (48), 130 (30). HRMS (EI) calculated for $C_{18}H_{13}N$ [M^+] 243.1048: found 243.1042.

3-p-tolylpyridine (**Table 4.6, entry 2**).



Preparation of this compound in accordance with **General Procedure A** using the following materials: 3-pyridyl diethylcarbamate (58 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5mmol), tri(*p*-tolyl) boroxine (103 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours complete conversion was observed by TLC. Purification of the crude was performed using flash chromatography, silica column, gradient elution of 5:1 to 2:1 (hexanes: ethyl Acetate + 2%NEt_3) over 200 mL to afford the product (87%, 44 mg, 0.26 mmol) as a light yellow oil. ^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.75 (d, *J* = 1.31 Hz, 1H), 8.47 (d, *J* = 3.76 Hz, 1H), 7.80-7.70 (m, 1H), 7.39 (d, *J* = 8.10 Hz, 2H), 7.25-7.22 (m, 1H), 7.22-7.16 (m, 2H), 2.33 (d, *J* = 9.59 Hz, 3H). Spectra match those previously reported.[54]

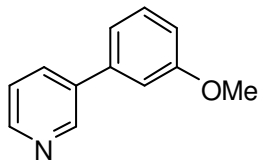
3-(4-methoxyphenyl)pyridine (**Table 4.6, entry 3**).



Preparation of this compound in accordance with **General Procedure A** using the following materials: 3-pyridyl

diethylcarbamate (58 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5mmol), tri(*p*-Methoxyphenyl) boroxine (116 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours complete conversion was observed by TLC. Purification of the crude was performed using flash chromatography, silica column, gradient elution 5:1 to 3:1 (Hexanes/ Ethyl acetate + 2% NEt_3) over 200 mL to afford the product (84%, 47 mg, 0.25 mmol) as a light yellow oil. ^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.81 (d, *J* = 1.74 Hz, 1H), 8.54 (dd, *J* = 4.78, 1.51 Hz, 1H), 7.83 (ddd, *J* = 7.91, 2.27, 1.69 Hz, 1H), 7.54-7.50 (m, 2H), 7.33 (ddd, *J* = 7.89, 4.81, 0.69 Hz, 1H), 7.03-6.98 (m, 2H), 3.86 (s, 3H). Spectra match those previously reported.[54]

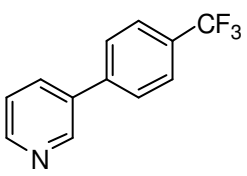
3-(3-methoxyphenyl)pyridine (**Table 4.6, entry 4**).



Preparation of this compound in accordance with **General Procedure A** using the following materials: 3-pyridyl diethylcarbamate (58 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5mmol), tris(3-methoxyphenyl) boroxine (117 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours complete conversion was observed by TLC. Purification of the crude was performed using flash chromatography, silica column, gradient elution 5:1 to 3:1 (Hexanes/ Ethyl acetate + 2% NEt_3) over 200 mL to afford the product (65%, 36 mg, 0.19 mmol) as light yellow oil. ^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.84 (s, 1H), 8.58 (d, *J* = 3.99 Hz, 1H), 7.91-7.81 (m, 1H), 7.43-7.30 (m, 2H), 7.15 (d, *J* = 8.02 Hz, 1H),

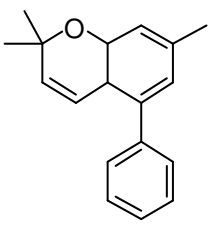
7.11 (dd, *J* = 11.37, 9.26 Hz, 1H), 6.93 (td, *J* = 12.63, 6.31, 6.31 Hz, 1H), 3.86 (s, 3H). Spectra match those previously reported.[55]

3-(4-(trifluoromethyl)phenyl)pyridine (**Table 4.6, entry 5**).



Preparation of this compound in accordance with **General Procedure A** using the following materials: 3-pyridyl diethylcarbamate (58 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg, 1.5 mmol), tris(4-triflouromethylphenyl) boroxine (150 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 20 hours complete conversion was observed by TLC. Purification of the crude was performed using flash chromatography, silica column, gradient elution 7:1 to 5:1 (hexanes/ ethyl acetate + 2% NEt_3) to afford the product (70%, 47 mg, 0.21 mmol) as a light yellow oil. ^1H NMR (400 MHz, *CDCl₃*) δ ppm 8.85 (d, *J* = 1.40 Hz, 1H), 8.64 (d, *J* = 3.76 Hz, 1H), 7.92-7.84 (m, 1H), 7.73 (d, *J* = 8.32 Hz, 2H), 7.70-7.63 (m, 2H), 7.39 (dd, *J* = 7.72, 4.82 Hz, 1H). Spectra match those previously reported. [54]

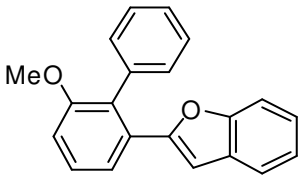
2,2,7-trimethyl-5-phenyl-4a,8a-dihydro-2H-chromene (**4.26)**



Preparation of this compound in accordance with **General Procedure A** using the following materials: phenyl diethylcarbamate (87 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318 mg,

1.5 mmol), triphenylboroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M). The reaction was stirred at 150 ^oC, after 5 hours no further conversion to the product (67%) was observed by GC/MS. Purification of the crude was performed using flash chromatography, silica column, hexanes as eluent to afford the product (56%, 42 mg, 0.17 mmol) as a light yellow oil. ^1H NMR (400 MHz, *CDCl₃*) δ ppm 7.31 (d, *J* = 6.85 Hz, 2H), 7.25 (s, 1H), 6.59 (d, *J* = 8.77 Hz, 2H),6.21 (t, *J* = 9.70, 9.70 Hz, 2H), 5.41 (dd, *J* = 19.89, 9.98 Hz, 2H), 2.23 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, *CDCl₃*) δ ppm 140.0 (1C), 139.4 (1C), 138.7 (1C), 129.6 (2C), 129.3 (2C), 128.0 (2C), 127.0 (2C), 122.9 (1C), 120.7 (1C), 116.4 (1C), 116.1 (1C), 75.2 (1C), 27.7 (3C), 21.4 (1C); IR (film CH_2Cl_2) V_{max} cm^{-1} 3028, 2974, 2923, 1607, 1561, 1496, 1453, 1388, 1274, 1360, 1323, 1295, 1215, 1137, 1110, 1017, 895, 868, 847, 7834, 767, 702, 650, 602; LRMS (EI) (*m/z)* (%), 250[M^+](15), 236(20), 235(100), 165(12); HRMS (EI) calculated for $C_{18}H_{18}O$ [M^+] 250.1358: found 250.1354.

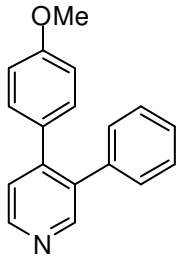
2-(6-methoxybiphenyl-2-yl)benzofuran (**4.28**)



Preparation of this compound in accordance with **General Procedure A** using the following materials: 2-(benzofuran-2-yl)-6-methoxyphenyl diethylcarbamate (102 mg, 0.3 mmol), $NiCl_2(PCy_3)_2$ (10 mg, 0.015 mmol), anhydrous K_3PO_4 (318mg, 1.5 mmol), triphenyl boroxine (90 mg, 0.29 mmol), PCy_3HBF_4 (11 mg, 0.03 mmol), *o*-xylene (1.5 mL, 0.2M The reaction was stirred at 150 ^oC, after 5 hours no further conversion to the product (52%) was observed by GC/MS. Purification of the crude was performed using Prep TLC

developed in hexanes to afford the product (21%, 19 mg, 0.06 mmol) as a colorless waxy solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.63 (d, *J* = 7.92 Hz, 1H), 7.42-7.29 (m, 5H), 7.23-7.16 (m, 3H), 7.13 (dd, *J* = 15.30, 7.87 Hz, 1H), 7.03 (t, *J* = 7.45, 7.45 Hz, 1H), 6.92 (d, *J* = 8.20 Hz, 1H), 5.51 (s, 1H), 3.68 (s, 3H); ^{13}C NMR (101 MHz, *CDCl$_3$*)δ ppm 157.2 (s,1C), 154.4 (s,1C),153.9 (s,1C), 137.3 (s,1C), 130.0 (s,3C), 128.6 (s,1C),128.4 (s,2C), 127.3 (s,1C), 124.1 (s,1C), 122.5 (s,1C),120.9 (s,1C), 119.8 (s,1C),111.0 (s,2C),110.82 (s,2C), 105.91 (s,1C), 55.98 (s,1C); IR (film) V_{max} cm^{-1} 3053, 3011, 2958, 2926, 2921, 2836, 1578, 1145, 1432, 1309, 1262, 1240, 1172, 1117, 1103, 1031, 934, 822, 796, 755, 703. LRMS (EI) (*m/z)* (%) 300[M$^+$] (100), 239(25), 301(270), 269(21); HRMS (EI) calculated for $C_{21}H_{16}O_2$ [M$^+$] 300.1150: found 300.1151; m.p. 130^{o}C sharp (hexanes).

4-(4-methoxyphenyl)-3-phenylpyridine (**4.30**)



Preparation of this compound in accordance with **General Procedure A** using the following materials: 4-(4-methoxyphenyl)pyridin-2-yl diethylcarbamate (64 mg, 0.21 mmol), $NiCl_2(PCy_3)_2$ (7.59 mg, 0.011 mmol), anhydrous K_3PO_4 (227.9 mg, 1.07 mmol), triphenyl boroxine (64 mg, 0.20 mmol), PCy_3HBF_4 (7.9 mg, 0.021 mmol), *o*-xylene (1.07 mL, 0.2M), stirred at 150^{o}C for 2 hours. Reaction was stopped when starting material was no longer observed by TLC. Purification of the crude was performed using flash chromatography, silica column, elution 5:1 to 2:1 (hexanes/ ethyl acetate + 2% NEt_3) to afford the product (91%, 48 mg, 0.18 mmol) as a light orange oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.57-8.53

(m, 2H), 7.28 (d, J = 5.03 Hz, 1H), 7.23 (td, J = 10.30, 5.18, 5.18 Hz, 3H), 7.17-7.09 (m, 2H), 7.09-7.00 (m, 2H), 6.75 (d, J = 8.78 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (400 MHz, *$CDCl_3$*) δ ppm 159.3 (1C), 150.9 (1C), 148.6 (1C), 147.3 (1C), 137.9 (1C), 135.6 (1C), 130.7 (1C), 130.5 (2C), 129.7 (C), 128.3 (2C), 127.2 (1C), 124.4 (1C), 113.7 (2C), 55.1 (1C); IR (film CH_2Cl_2) V_{max} cm^{-1} 2836, 1608, 1586, 1515, 1496, 1474, 1444, 1398, 1295, 1250, 1178, 1110, 1042, 1023, 1006, 827, 808, 781, 756, 701; EIMS (*m/z (%)*) 218[M^+](100), 69(99), 131(87), 263(45), 100(28), 501(15), 217(17), 169(12); HRMS (EI) calculated for $C_{18}H_{15}NO$ [M^+] 261.1154: found 261.1142.

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Chapter 5

Chiral Periodic Mesoporous Organosilica

5.1 Introduction to Periodic Mesoporous Organosilica

As described in chapter 2, the introduction of organic functionality to purely siliceous materials either through grafting or co-condensation is powerful a method for the synthesis of composite materials. However, this method is disadvantaged by the inhomogeneous distribution of organic functionality[1] and the deterioration of long range order and pore structure with high organic loadings.[2]

In contrast, periodic mesoporous organosilica materials (PMOs) offer an alternative method for the production of composite materials, producing entirely new materials from the polymerization of bridged silsesquioxanes precursors.[3] Unlike grafted or co-condensed materials, 100 % of the organic functionality is homogeneously distributed within the structure. PMOs can be prepared with narrow pore size distributions depending on the organic spacer,[4] and properties[2] such as hydrophobicity, optical clarity, porosity, stability, chemical resistance, and dielectric constant, can be tuned by altering the organic bridging unit. Demonstrated first by Shea and coworkers in disordered materials[5], a number of materials have now been prepared using different bridged silsesquioxanes either with or without surfactant to introduce porosity and structure (Figure 5.1).[6]

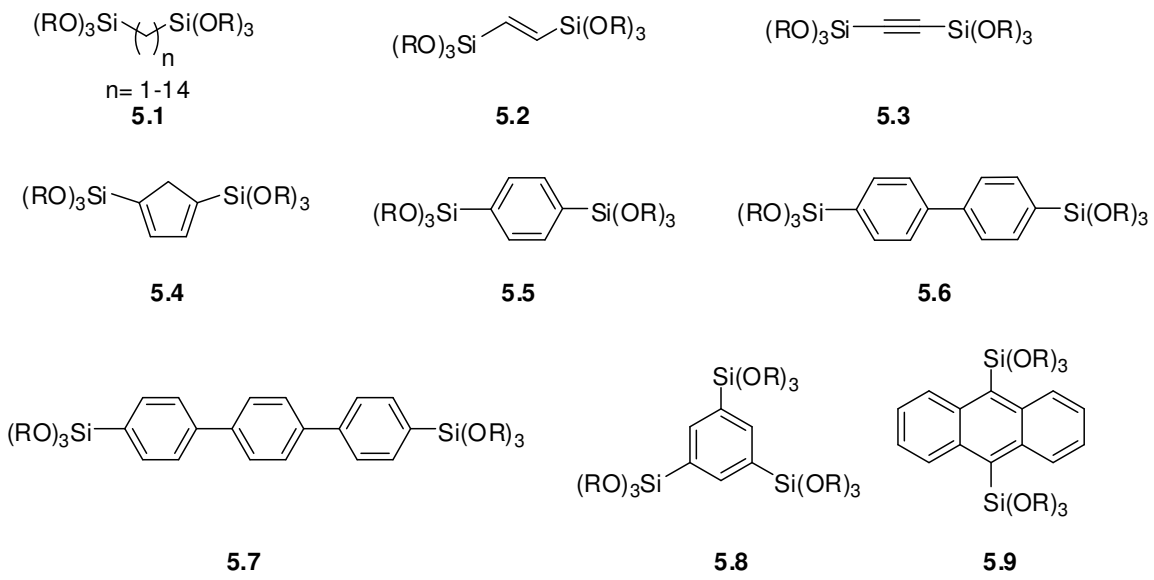


Figure 5.1 Bridged silasesquioxanes used the preparation of PMOs.

The simplest PMO is methylenesilica (**5.1**, n=1),[7] which is intriguing because the methylene bridge is isoelectronic for oxygen in the SiO_2 network. Interestingly, it is more conformationally restricted[8] and upon heat treatment at 350-600^{o}C, the bridging methylene unit is converted to a terminal methyl group, without any loss of the mesostructure, simultaneously increasing the hydrophobicity of the material.[7]

The length of alkyl-bridged silasesquioxanes **5.1** has been shown to have a dramatic effect on the materials gelation time and porosity.[9,5] Gelation time is noticeably retarded for monomers of (**5.1,** n = 3-4), by the intramolecular formation of cyclic intermediates which are stable to condense into polymeric structures.[10,9b]

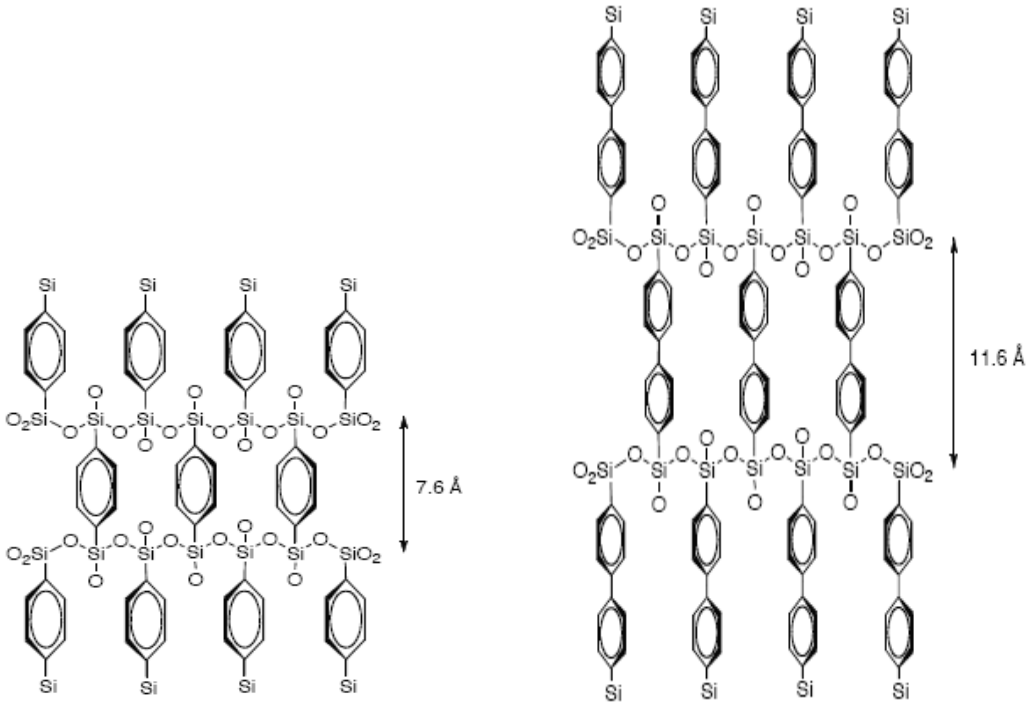
PMOs composed of ethylene bridged silasesquioxanes **5.2** have been prepared by both Stein and Ozin.[11,4] Both groups attempted to brominate the alkene: Stein employed

gaseous bromine for 18h, demonstrating that chemical modification of the alkene, without disruption of the porosity of the material as assessed by XRD and TEM. However, incomplete bromination of the alkene was detected by solid state CP MAS ^{13}C NMR.[11] Ozin brominated the alkene in refluxing dichloromethane for eight days, after which NMR analysis showed complete disappearance of the alkene, however only 10% bromination was detected by chemical analysis. Significantly, these studies highlight that post-condensation chemical modification of the PMO is possible; however the accessibility of the organic groups may pose a problem.

The incorporation of rigid arylene bridged monomers into ordered silasesquioxanes (**5.4 -5.9**), has been demonstrated by Inagaki and others.[13] These materials are of interest as it is proposed that π-π stacking leads to crystallinity in the pore walls, although this has not been definitively proven (vide infra). A molecularly ordered wall may enhance the materials' application in electronic, optical, and sensing fields.[2]

Most effort has been focused on PMOs prepared from the phenylene **5.5** and biphenylene **5.6** monomers. The materials prepared from these monomers are characterized by high surface areas and pore diameters ranging from 10 to 50 Å.[12] However, it was Inagaki[13] who first demonstrated a PMO with crystal-like organization in the materials derived from the phenylene monomer **5.5**. In addition to the peaks attributed to the 2D hexagonal mesoscopic order, powder XRD analysis displayed sharp peaks with a periodicity of 7.6 Å, which is attributed to the repeat distance of the silyl

phenylene unit (**A**, Figure 5.2). Further functionalization of this material was accomplished by sulfonation, resulting in a high performance solid phase acid catalyst. Similar results were later obtained with a PMO prepared from the biphenylene monomer **5.6**, resulting in pXRD peaks with a spacing of 11.6 Å (**B**, Figure 5.2).[14] Although pXRD evidence is compelling there exists no definitive evidence crystallinity between the organic groups however recent fluorescent studies indicate interactions between the organic groups in the pore walls.[15]



A **B**

Figure 5.2 Representation of PMO crystallinity, A) Phenylene PMO, B) Biphenylene PMO.

5.2 Chiral PMOs

One significant advantage of PMOs is that a variety of organic groups can be incorporated into the walls, which will have a large effect on the materials properties. As noted in (Figure 5.1) most of the monomers used to date are quite simple, which stems from issues with self condensation/oligomerization in flexible systems, to issues with the difficulties associated with synthesizing complex bis siloxanes. There are, however, a few examples where the polymerization of chiral monomers can be used to generate chiral PMOs.[18,19] In addition, chiral materials can be prepared though the use of chiral templating agents[16]

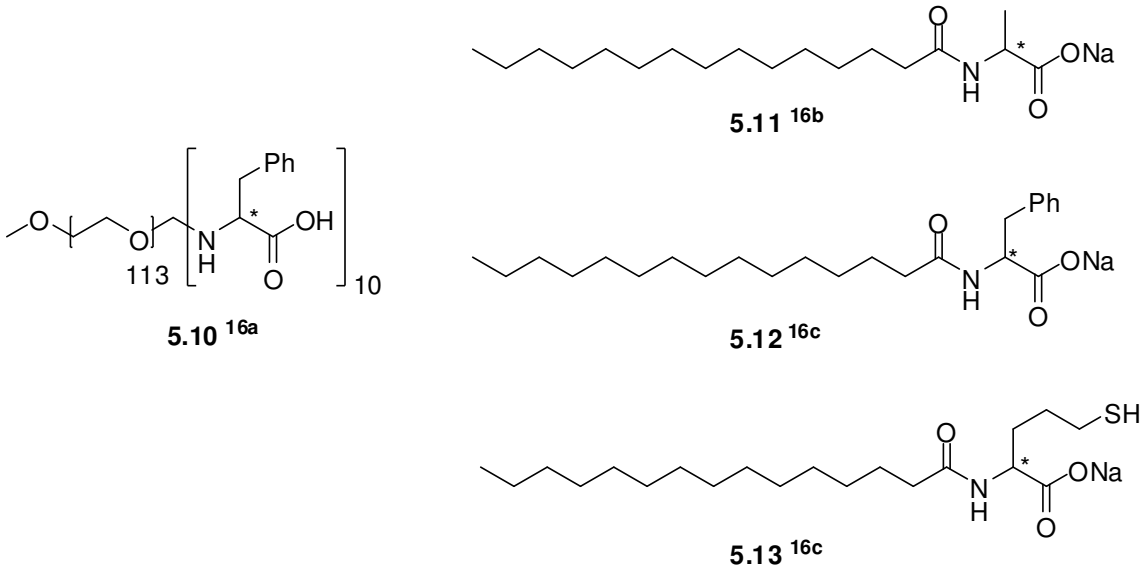


Figure 5.3. Chiral Surfactants employed in the preparation of chiral mesoporous silica.[16]

One of the simplest methods is to generate a chiral material is to use a chiral template. A number of amino acid based chiral surfactants have employed in the synthesis of chiral silica-based materials[16] (Figure. 5.3).

Mastai[16a] and coworkers prepared chiral silica-based materials utilizing chiral phenylalanine based block co-polymer surfactant **5.10**, which afforded a two dimensional hexagonally ordered material. After extraction, chirality was demonstrated by the preferential adsorption of one enantiomer of a racemic mixture of amino acids. Materials prepared with D or L phenylaniline-based surfactant preferentially adsorbed the matching D/L valine or alanine, with enantiomeric excesses of up to 40% reported after 16 hours of exposure.

Using the amino acid-based surfactant **5.11** as a templating agent, Che and coworkers[16b] were able to prepare 2D-hexagonally ordered materials using APTES, TMAPS, and TEOS. Interestingly the material displayed a helical twist which could be observed via TEM and SEM with a pitch length of ~1.5 μm (Figure 5.4). Enantiopurity was determined by counting the number of particles with twists in the same direction, an excess of left hand helixes were observed with the L-aniline surfactant, right hand helixes were produced with D-aniline, in an approximately (30 – 50)% ee.[16c] Enantiomeric excess of greater than 90% were obtained using surfactants **5.12** and **5.13** based on other amino acids.[16d] In an attempt to increase enantiopurity further, the material was condescended at temperatures of 0^{o}C, however this resulted in the production of chiral ribbons with a disordered pore structure.[16d]

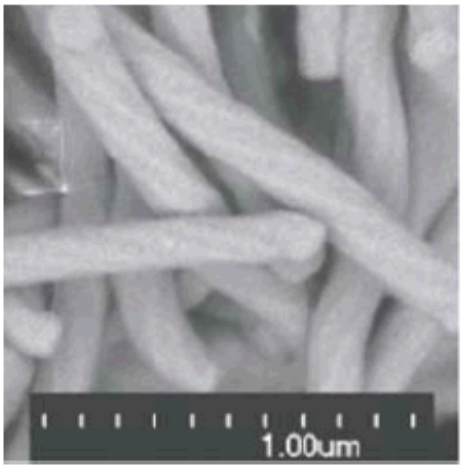
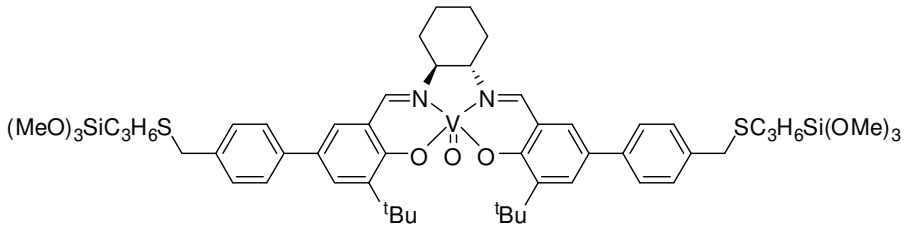


Figure 5.4 SEM image of chiral helixes. Reproduced from ref 14b.

The work by Tatsumi and coworkers[17] illustrates the important point that helical structures can be formed without the presence of any chiral additives. They were able to form racemic helixes using a mixed surfactant system of FC-4911 and CTAB. Because no chirality was introduced into the system, an equal number left handed and right handed helices were observed.

The polymerization of chiral silasesquioxanes to create chiral PMOs is an alternative method. The first example of a chiral PMO prepared by this method was by Corma and coworkers[18] condensing the chiral vanadium complex **5.14** with TEOS (Scheme 5.5). Although technically considered to be a PMO, this material was largely composed of silica, since monomer **5.14** made up only 5-15% of the material.



5.14

Figure 5.5. Chiral Vanadium Complex Silasesquioxane.

The resulting PMO was able to catalyze the enantioselective cyanosilation of benzaldehyde with enantioselective excesses of up to 30%. However, when **5.14** was grafted onto the pore walls, the enantiomeric excess rose to 63%. The loss of enantioselectivity in the PMO material was attributed to steric interactions of the catalyst within the pore wall.[18] Since then a number of chiral precursors have been used to prepare chiral PMOs (Scheme 5.6).[19]

In almost all cases, the chiral precursors contain large flexible siloxy linkers, requiring a large dilution of inorganic silica to maintain order and porosity. This raises the question of how one defines a chiral material. Certainty there exist numerous examples of grafting of chiral organic groups onto inorganic supports,[20] but can materials prepared by co-condensation of chiral silasesquioxanes with inorganic silica constitute a chiral material, or simply chiral functionalities suspended in an achiral inorganic matrix? In the above example, it would appear that grafting of **5.14** is more efficient.

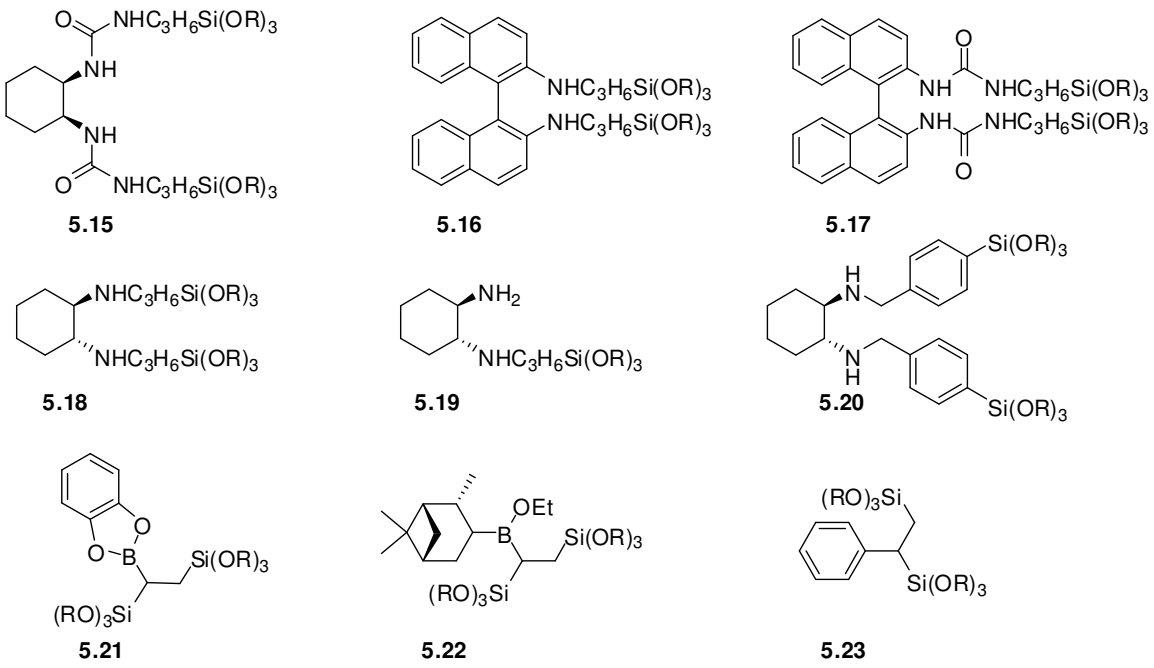


Figure 5.6. Various Chiral Silasesquioxanes.

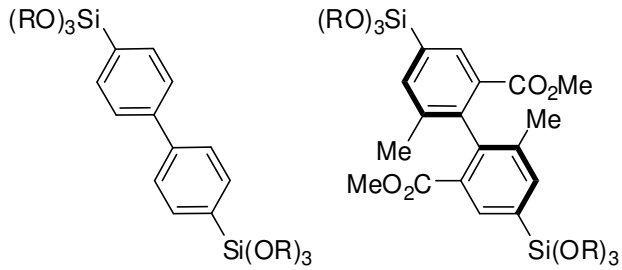
PMOs derived from **5.21** have been prepared without the need for a co-silica source.[21] Chirality was detected by circular dichroism, however the since no method was employed to determined the enantiopurity of **5.21**, derived from a rhodium catalyzed asymmetric hydroboration, the true enantiopurity of the material cannot be established.

Ozin and co-workers[19f] employed the chiral borane monomer **5.22** under acidic conditions. Materials produced solely from **5.22** had low surface areas and were microporous. Dilution with TEOS was required to generate ordered mesoporous materials, boron was removed by aminolysis.

Utilizing the chiral monomer **5.23**, Inagaki's group[19g] prepared microporous materials under acidic conditions, and the chirality of **5.23** was observed to remain intact.

Although high quality mesoporous materials were produced under basic conditions, complete racemization of **5.23** was observed.

Current research in the Crudden group has focused on biphenylene-based PMOs.[22] The biphenylene was chosen due to its prochiral nature; the biphenyl rings display axial chirality which rapidly interconvert.[23] The strategy is a unique one, incorporating an axially chiral dopant **5.24** (Figure 5.7) that is co-condensed with the biphenylene bulk materials, to affect a twisting of the organosilica network propagated through π-π stacking.

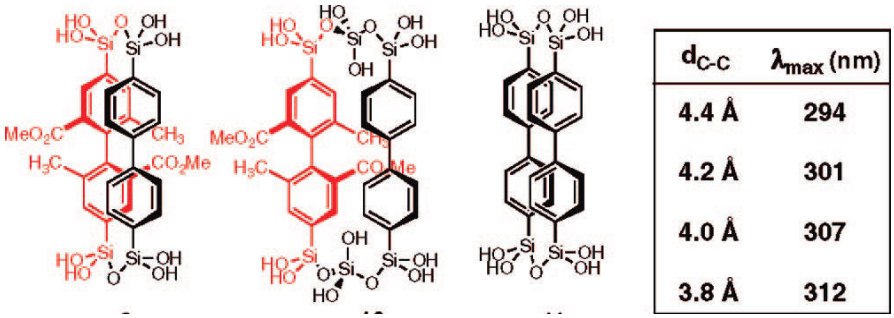


5.6 **5.24**

Figure 5.7. Silasesquioxanes used to Generate Chiral Materials.

Chirality in these materials was measured using solid state CD spectroscopy.[24] In the doped materials, a red shifted peak was observed at a V_{max} of 315 nm.[20] Using the opposite enantiomer the mirror image was observed. Materials prepared with **5.24** co condensed with TEOS as the bulk was observed to display blue shifted peak at 260 nm, resembling that of the monomer itself. This suggests that the signal at 315 nm results from interactions between **5.6** and **5.24** in the material which leads to new chiral

aggregate species in the material, a proposal that was confirmed using DFT calculations (Figure.8). [22]

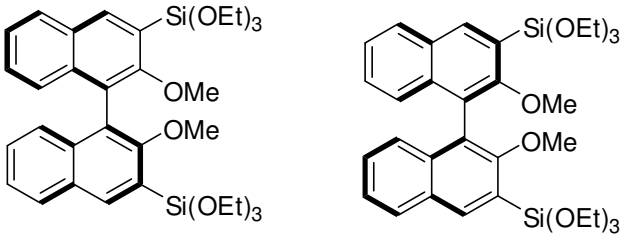


$d_{C\text{-}C}$	λ_{max} (nm)
4.4 Å	294
4.2 Å	301
4.0 Å	307
3.8 Å	312

Figure 5.8. Images reproduced from Ref.22

5.3 Aims of Research

The synthesis of **5.24** was lengthy and inefficient, requiring an HPLC-based separation of the enantiomers.[25] Thus we turned our attention to binaphthol based dopants such as **5.25** which are more easily prepared (Figure 5.9). Binaphthol was chosen as it has been extensively used as a chiral agent[26] and is commercially available in both enantiomeric forms, eliminating the need for preparatory chiral HPLC purification.[25]

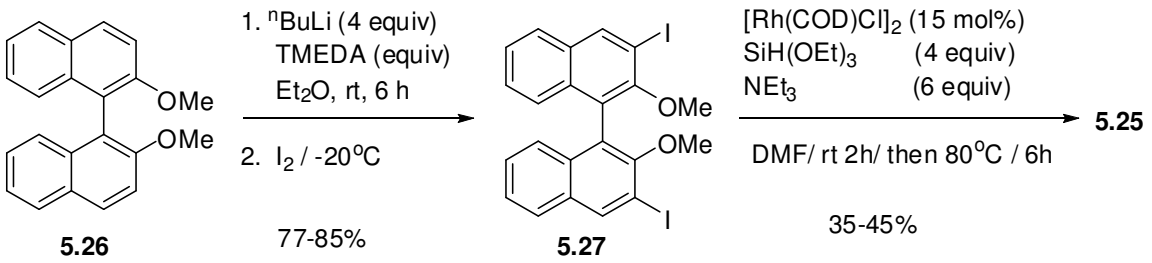


5.25 (S) **5.25 (R)**

Figure 5.9 Binaphthol Chiral Dopant.

5.4 Results and Discussion

The concise synthesis of the desired monomer (Scheme 5.1) combines directed *ortho* metalation[27] and a rhodium catalyzed coupling[28] to achieve the synthesis of **5.25** in 2 steps (Scheme 5.1). Although **5.26** is commerically available, it is easily prepared from alkylation of the corresponding binaphthol in quantitative yield.[29] Attempts to further abbreviate the synthesis via direct quench of the anionic intermediate leading to **5.27** were attempted, however, work up and isolation of the sensitive siloxy group proved troublesome. The synthesis of enantiomerically pure **5.25** is exactly the same as the racemic.



5.26 **5.27**

Scheme 5.1 Synthesis of binaphthol based silasesquioxane 5.25.

With sufficient quantities of **5.25** in hand, preliminary work began to co-condense 4,4'-bis-(triethoxysilyl)biphenyl **5.4** with the racemic of **5.25** in a 85:15 wt % mixture using a variety of conditions and surfactants (Table. 5.1).

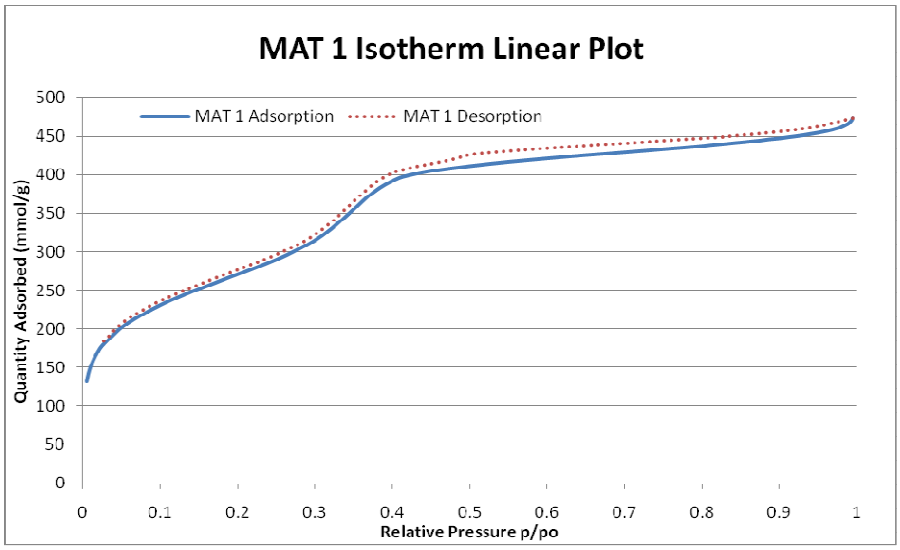
Table 5.1. Conditions screened for initial condensation of material

MAT	Surfactant	Condensation	Aging	SA m^2/g^a	Avg. Pore Diameter[b]	Avg. Pore Volume[c]
1	Brij 76/ HCl	60°C / 20 h	80°C / 24h	978	22.7	0.676
2	C_{18}TABr / NaOH	rt /20 h	95°C / 20h	669	27.8	0.565
3	P123/ HCl	40°C / 24 h	95°C / 20h	777	36.6	0.725
4	F127 / HCl	40°C / 24 h	100°C / 24h	-	-	-

a] BJH adsorption cumulative pore diameter. [b] BET surface area. [c] BJH adsorption cumulative pore volume

Employing Brij 76 as the surfactant **MAT1** resulted in an ordered porous material that incorporated the monomer **3** with pore sizes of ca. 22 Å (Figure.10). Analysis by powder X-ray diffraction reveals a peak below 2θ with a *d*-spacing of 55-60Å indicating that the material is mesoporous (Figure.11). The TEM image shown in (Figure 12) reveals a 2D ordered mesostructure (Figure. 12). ^{29}Si CP MAS NMR (Figure. 13) displays only T-type resonances demonstrating that cleavage of the Si-C bonds did not occur. The presence of the binaphthol monomer was also confirmed by ^{13}C CP MAS NMR (figure. 13).

Under basic conditions, a material (**MAT2**) was obtained without incorporation of the binapthol monomer **3**, as determined by ^{13}C CP-MAS NMR. The use of block co-polymer surfactants such as P123 (**MAT3)** resulted in poorly ordered materials, whilst conditions using the surfactant F127 resulting in a minimal amount of condensed material recovered (**MAT4)**.



BJH Pore Diameter Å[a]	Surface Area m^2/g [b]	Pore Volume m^3/g[c]
22.7	978	0.676

a] BJH adsorption cumulative pore diameter. [b] BET surface area. [c] BJH adsorption cumulative pore volume

Figure 5.10 N_2 Adsorption of MAT1.

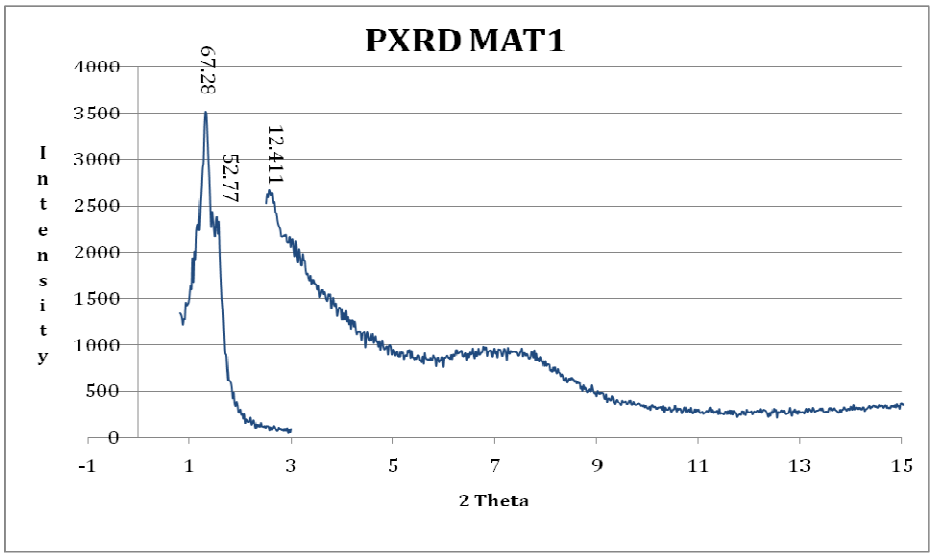


Figure 5.11. PXRD of MAT 1, Displaying a Mesostructure with *d*-spacing of 55-60Å.

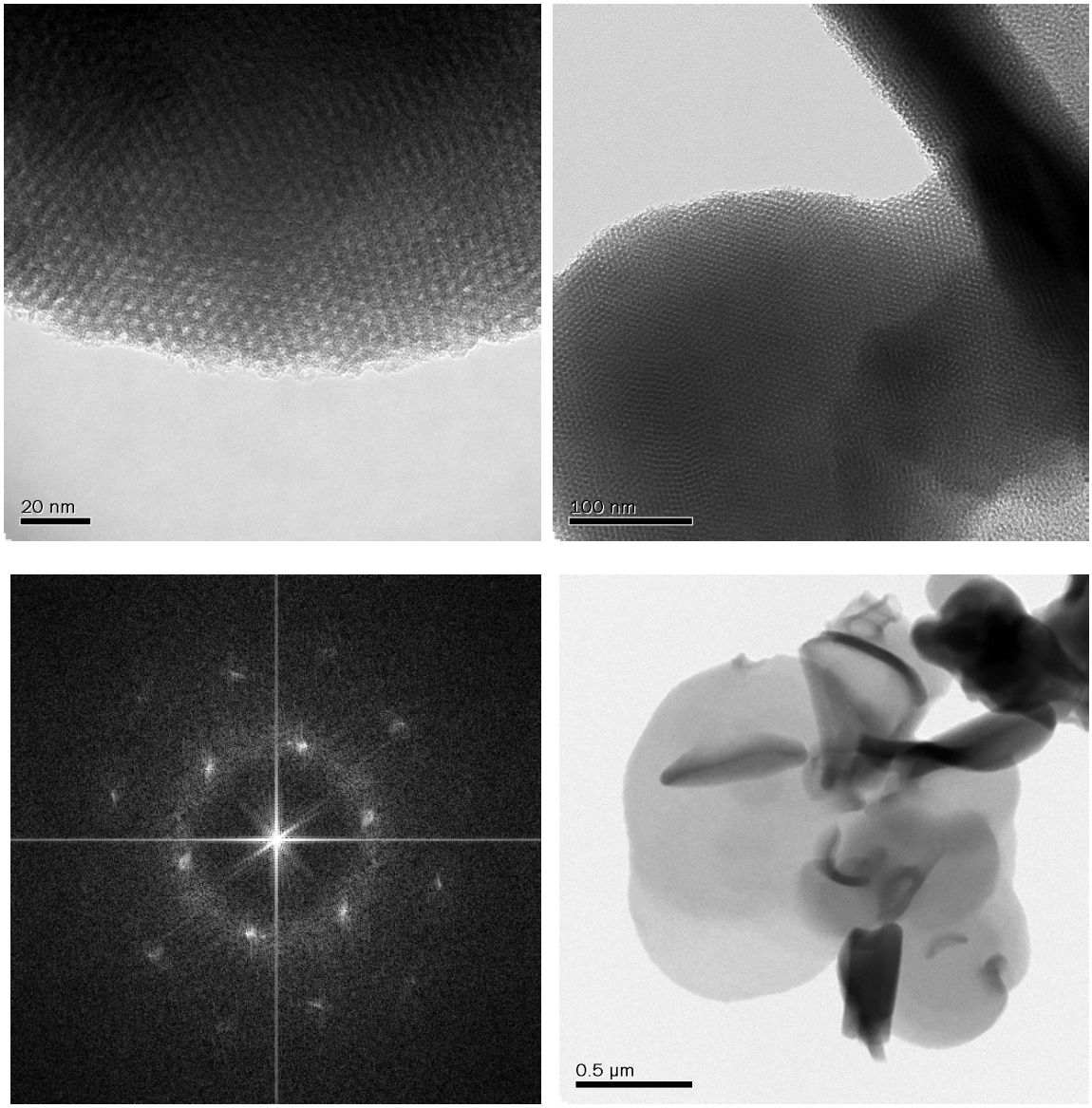


Figure 5.12. Selected TEM Images of MAT 1.

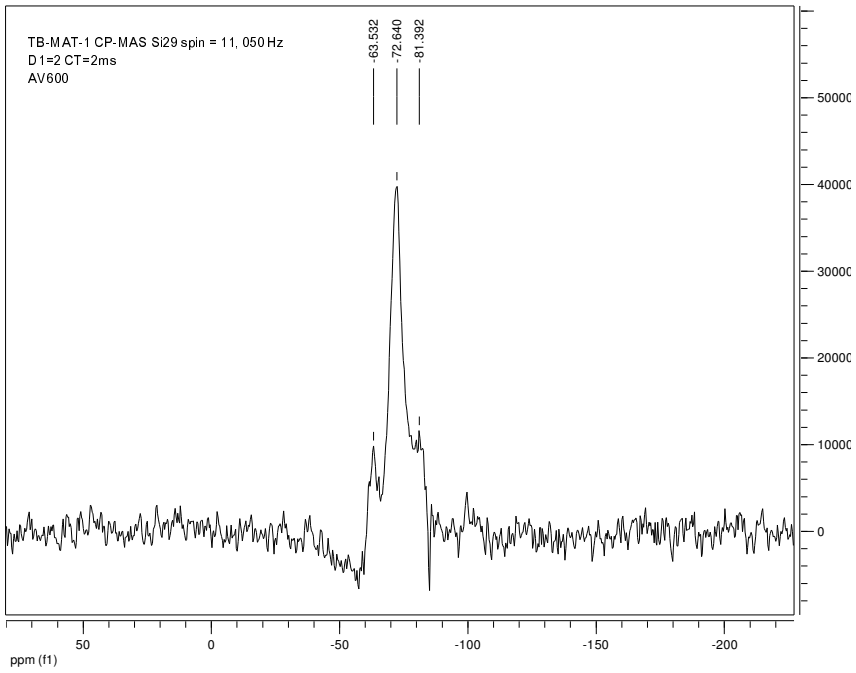


Figure 5.13. ^{29}Si CP-MAS NMR Mat 1

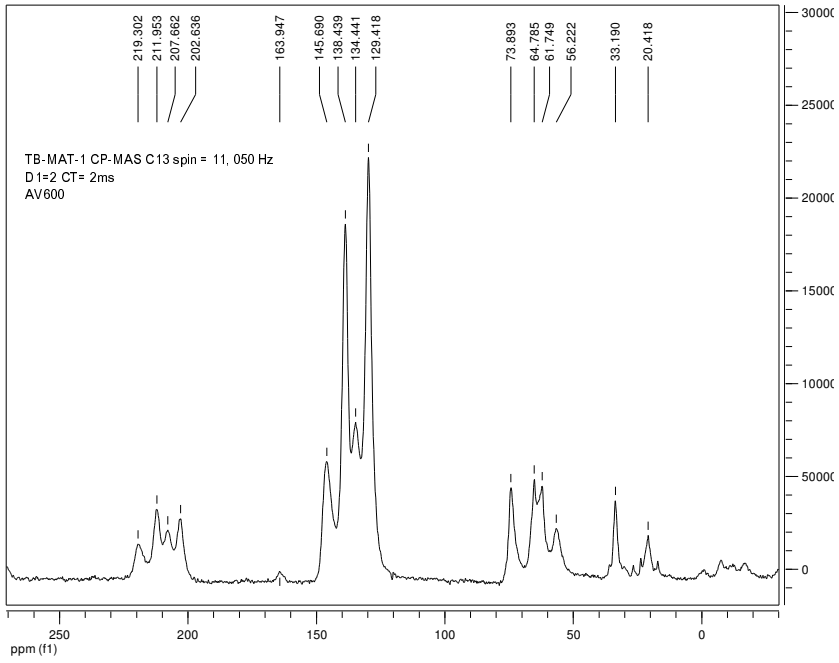


Figure 5.14. ^{13}C CP-MAS NMR [1] Mat 1.

Having identified a set of optimal conditions, well ordered porous materials were synthesized using the enantiomerically pure binaphthol dopant **5.25** in increasing amounts 5, 15%, 30%, and 100% wt% relative to biphenyl monomer **5.6** (Table. 5.2). Decreases in pore diameter and volume were observed as the loading of **5.25** was increased. Materials (**MAT 8 and 10**) underwent hydrothermal treatment,[30] which provided high quality materials. As expected based on previous results from the Crudden group[22] material prepared from 100% **5.25** displayed a marked reduction in surface area, pore diameter and volume. Materials co-condensed with TEOS as a comparison were also produced.

Table 5.2 Critical parameters of Materials 5-15.

MAT	Wt% 5.25	SA m2/g[a]	Avg. Pore Diameter[b]	Avg. Pore Volume[c]
5	5 (S)	957	26.9	0.760
6	5 (R)	878	27.9	0.711
7	15 (S)	838	22.6	0.563
8	15 (S)[d]	680	18.8	0.489
9	15(R)	897	22.8	0.596
10	15(R)[d]	916	25.3	0.665
11	30(S)	926	20.6	0.548
12	30(R)	818	19.4	0.454
13	100% (S)	376	17.6	0.191
14	15% (S)[e]	1015	22.6	0.570
15	5% (R)[e]	679	22.6	0.363

[a] BET surface area. [b] BJH adsorption cumulative pore diameter. [c] BJH adsorption cumulative pore volume. [d] Materials were treated hydrothermally.[e] Bulk material made up of TEOS.

Circular dichroism spectroscopy of both enantiomeric forms of the monomer **5.25** in ethanol displayed sigmoidal peaks at 225nm and 238 nm as shown Figure 5.15).

Materials prepared from the co-condensation of **5.25** in TEOS produced peaks similar to that of **5.25** yet broadened. Remarkably, monomer **5.25** could even be detected in concentrations as low as 5%.

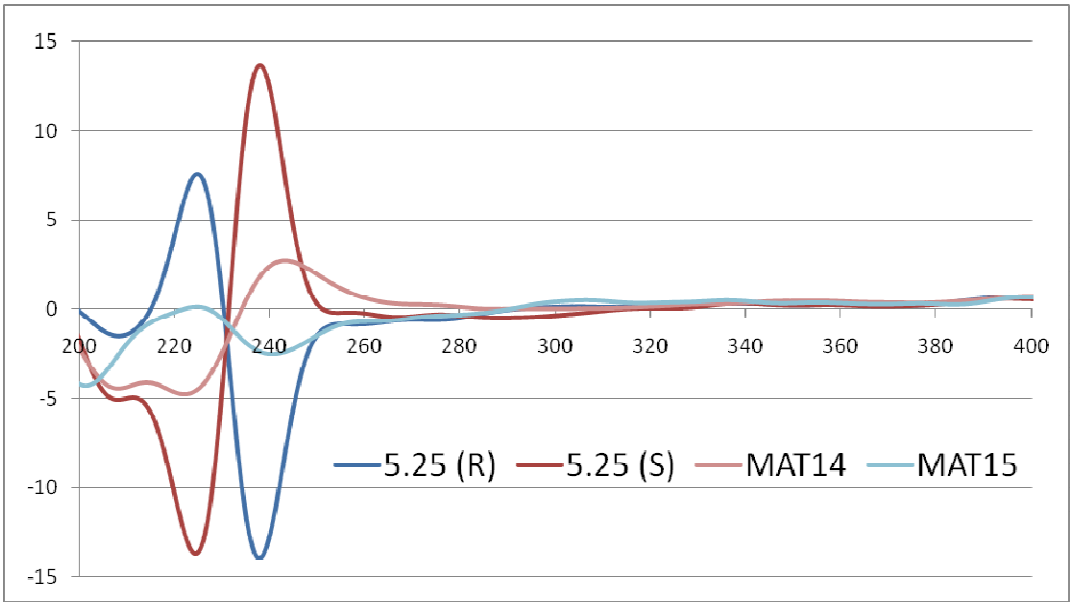


Figure 5.15. CD spectra of 5.25, and 5.35 in TEOS.

Analysis of the CD spectra for PMO materials (**MATs 5-12**) revealed a broad peak at ca. 340 nm. As previously observed for chiral biphenyl-based materials, this peak dominated the spectra increasing in intensity as the loading of **5.25** is increased. Small peaks at 225nm and 238 nm were observed, however in low intensity, however some clearly overlap with the signals for the binol monomer itself. Gratifyingly, mirror image CD spectra were obtained when the opposite enantiomer was used. Unlike materials previously prepared,[22] the spectra remained unchanged upon hydrothermal treatment. It

is also important to note that the CD spectra obtained as a KBr pellet or in various solvents remains relatively unchanged, however better reproducibility is obtained in ethanol.

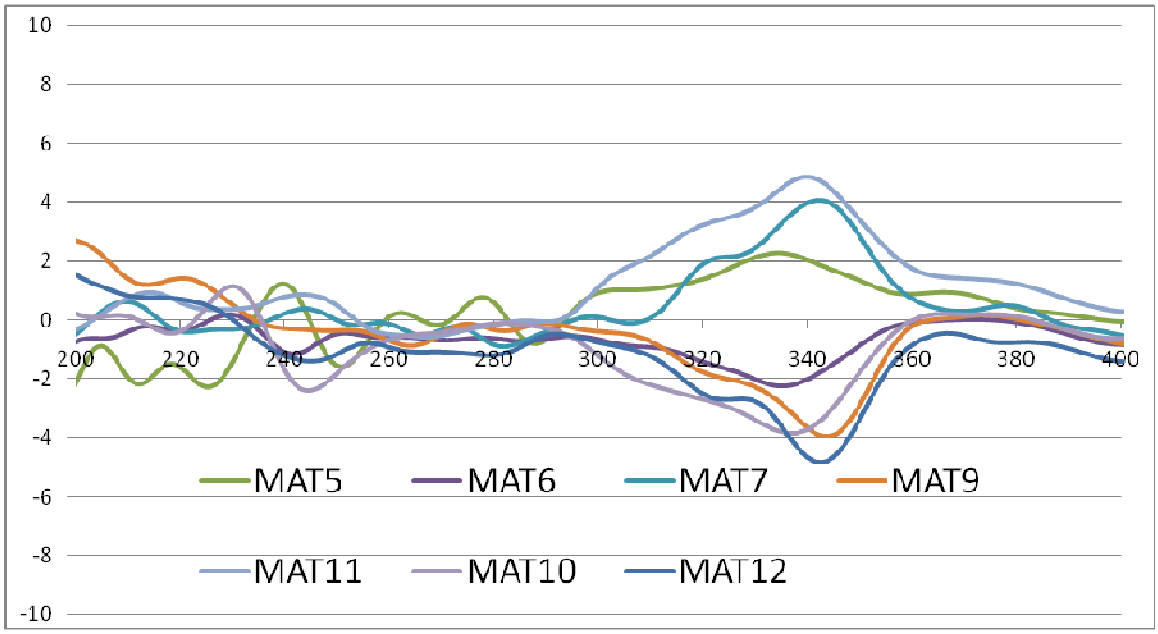


Figure 5.16. CD spectra of MATs (5-12) in EtOH.

The unique non linear arrangement of the siloxy groups of **5.25** prompted us to investigate how **5.25** transmits chirality to the biphenyl material. One possible structure that could affect a twisting in the biphenylene matrix is the direct complex (Figure. 5.17), resulting from **5.25** condensing with both siloxy groups of the biphenylene **5.6**. The spacer complex (Figure. 5.17) was also considered, in which **5.25** condenses with alternating biphenylenes, a model previously proposed by Inagaki.[14]. DFT calculations were performed in collaboration with Dr. Nicholas Mosey,[31] the structures of the complexes and the corresponding monomers were evaluated at the BhandHLYP/6-

31++G(d,p) level of theory,[32] and their CD spectra were evaluated using time-dependent density functional theory methods using the Gaussian 03 software package.[33]

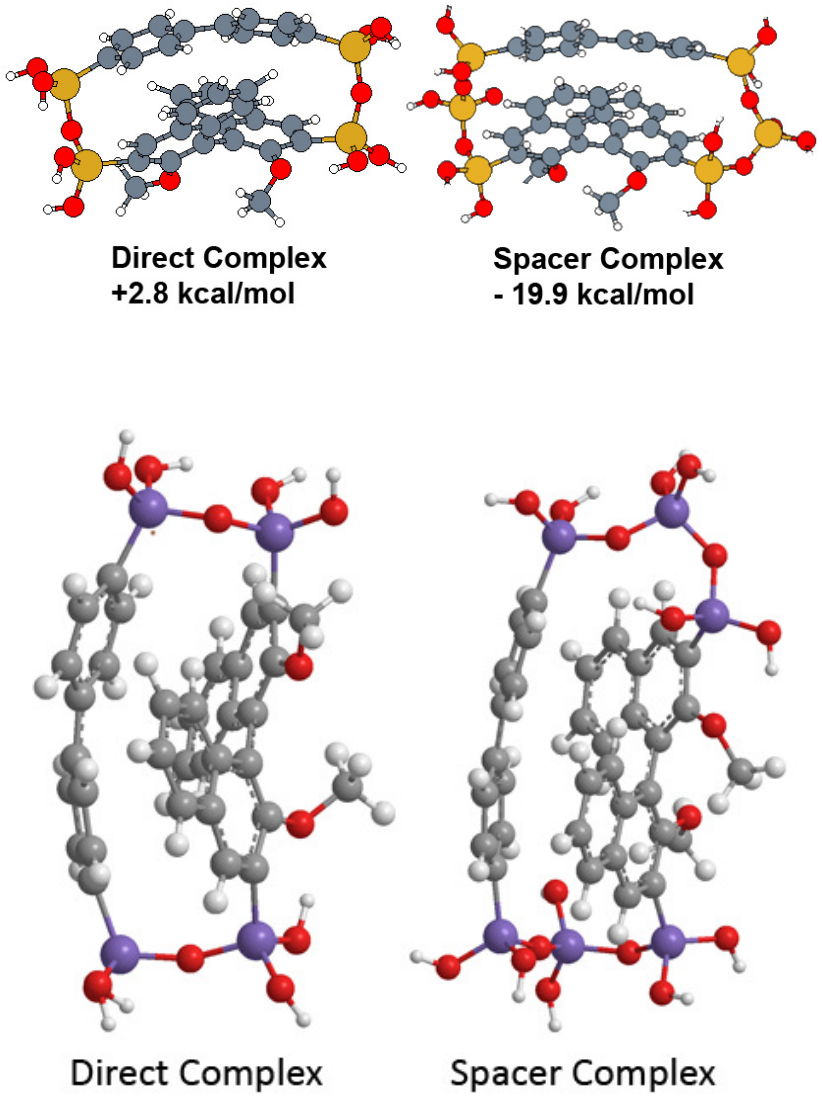


Figure 5.17. Optimized Geometries of the Direct and Spacer Complex.

The shape of the calculated CD spectrum of the binaphthyl monomer **5.25** (Figure 5.18), corresponds closely with the experimental spectrum; although, the calculated peaks are blue-shifted by ~25 nm. The spectra of the direct and spacer complexes are both red-shifted with respect to **5.25**, with peaks appearing in both spectra between 260 and 315 nm. Assuming these spectra are also blue-shifted by ~25 nm with respect to experiment, one can associate these peaks with those in the 300 to 340 nm region of the experimental spectra. The calculated spectrum of the direct complex exhibits a large peak at 230 nm that is not present in the calculated spectrum of the spacer complex or any of the experimental spectra in (Figure 5.18). The red shift of peaks found in the CD spectrum indicates that electronic delocalization between the adjacent biaryl rings is occurring, and that this transition results from a chiral species.

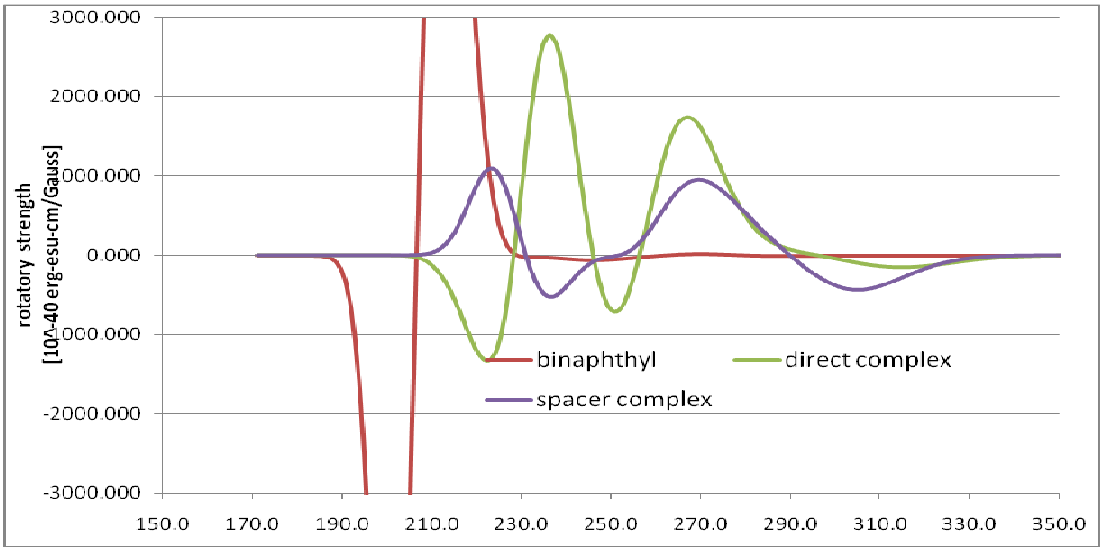


Figure 5.18. Simulated CD Spectra of the Direct and Spacer Complex's.

The results of the calculations suggests that the material does not have a structure consistent with that of the direct complex. This conclusion is supported by the energetics associated with forming direct and spacer complexes, which show that the direct complex is unstable (ΔE = + 2.8 kcal/mol) and the spacer complex is stable (ΔE = -19.9 kcal/mol) with respect to the reactants (Figure 5.17). It is important to note that these are fairly complex calculations which are an approximation, especially considering the uncertainty in both the experimental and calculated data.

The UV of the spectra of doped materials were also taken (Figure 5.19), is characterized by the presence of two peaks at 300 and 340 nm along with the small peaks at 240nm corresponding to the monomer **5.25**. It is currently not clear if the peak at 300 nm is present as a shoulder in the CD spectrum. Further work to obtain higher resolution CD spectra are being perused.

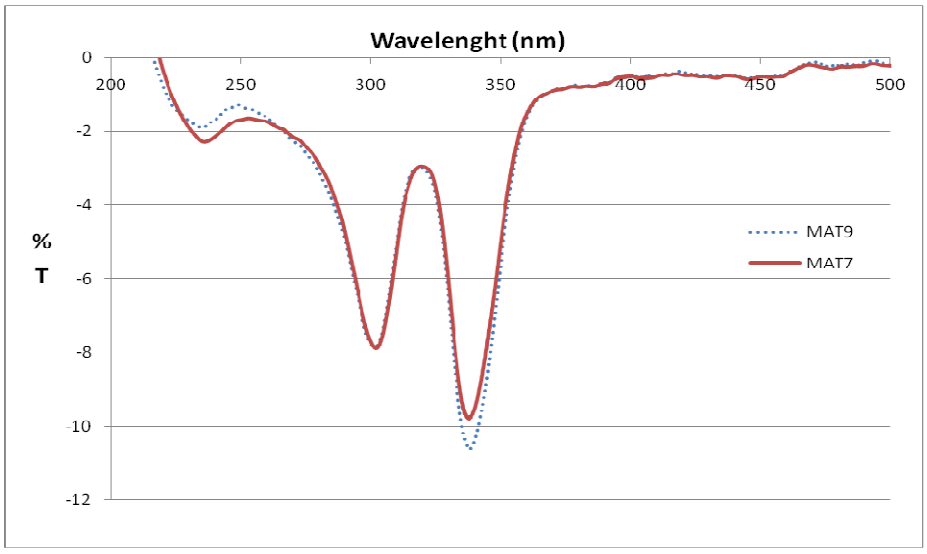


Figure 5.19. UV Spectra of MAT (7-9).

Considering the ease and cost effectiveness of this preparation we wished to explore these materials as chiral stationary phase in chiral chromatography. Initial attempts using powdered 100% chiral material **MAT13** were promising. Work performed in collaboration with Gibson and Oleschuk[34] using nano-HPLC columns resulted in slight separation of enantiomers (Figure. 20). The stationary phase appeared to have good selectivity, however poor column efficiency has been attributed to small particle size and inhomogeneity. The small particle size necessitated higher pressures causing broadening of the solute band resulting from poor mass transfer kinetics, increasing the C term in the Van Deemter equation. In addition deterioration of plug flow is also observed at higher pressures. Inhomogeneity of particle size also causes band broadening due to different path lengths, leading to an increase in the A term in the Van Deemter equation. We attempted to improve the efficiency by using electro osmotic flow instead of hydrodynamic pumping with limited success.

Ongoing work to improve column efficiency in collaboration with Du[35] has involved producing a templated monolith. While initial results using conditions adapted from Motokawa and coworkers[36] resulted in premature condensation, current work using using DMA as a solvent is ongoing and very promising.[37]

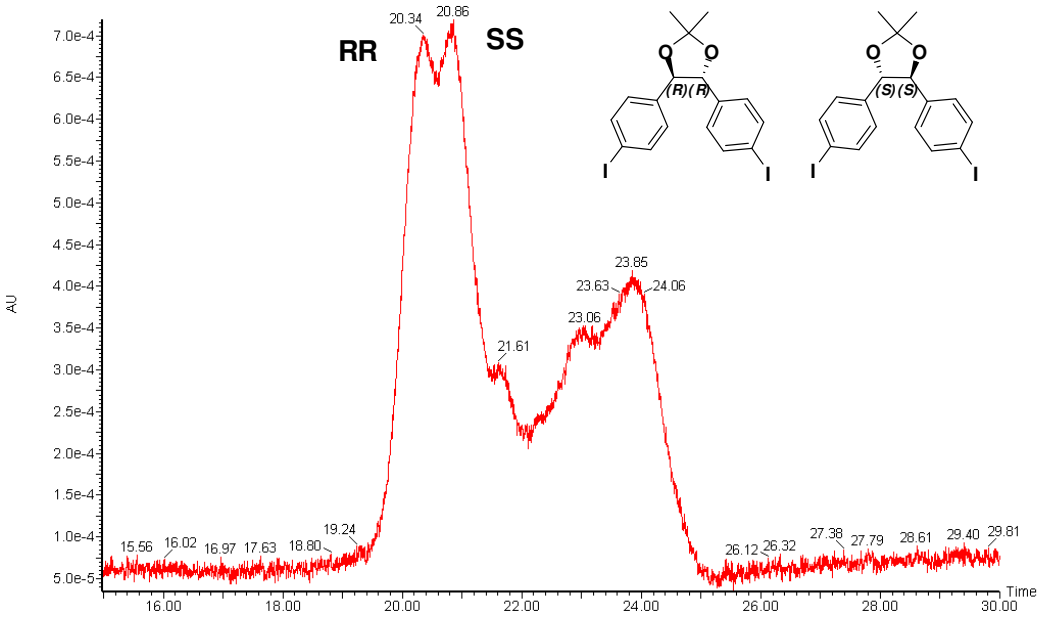


Figure 5.20. Initial Separation of Enantiomers.

5.5 Conclusions

The preparation of a binaphthol/binphenylene based PMO giving access to both enantiomers is demonstrated and represents the first work to incorporate **5.25** into mesoporous silica material. The chiral dopant **5.25** is not only relatively simple to prepare, but has been demonstrated to successfully co-condense with 4,4'-bistriethoxysilyl)biphenyl into a well ordered material without requiring the addition of inorganic silica. A variety of surfactants and conditions were tested, acidic conditions employing Brij 76 as a surfactant resulted in the ordered materials displaying mesoporosity, high surface areas, and incorporation of the binaphthyl monomer.

Materials were characterized by nitrogen absorption, TEM, CP-MAS NMR, and PXRD. Chirality in these materials were examined by circular dichroism spectroscopy, the presence of peaks considerably red-shifted from that of the chiral dopant **5.25** or **5.25** condensed in TEOS, indicates the transfer of chirality to the bulk matrix. Furthermore DFT calculations support transfer of chirality to biphenylene, however, exactly how this transfer occurs in unclear at the moment. Practical application of these materials as a chiral stationary phase is in progress and encouraging.

5.6 Experimental

5.6.1 General Methods

IR spectra were recorded as films in CH_2Cl_2 or as KBr pellets using a BONEM FT-IR spectrophotomer. NMR spectra were recorded on a Bruker Avance-300, 400, 500, or 600 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. Diethyl ether and THF were obtained anhydrous by forced passage through activated alumina in a Pure-Solv 400 solvent purification system (Innovative Technology, Inc.), whereas anhydrous DMF was purchased from Sigma-Aldrich Chemical Co. DMF used in Rh catalyzed reactions was degassed via freeze pump thaw method under argon. Alkyllithiums were purchased from Sigma-Aldrich and were titrated biweekly with *N*-benzylbenzamide to a blue endpoint. Anhydrous diisopropylamine and tetramethylethylenediamine were obtained from Sigma-Aldrich and were stored over KOH under argon. All water sensitive experiments were carried out under argon in flame-dried glassware, using syringe-septum and/or Schlenk techniques. Flash column chromatography was carried out using Silicycle Silia-P Flash Silica Gel.

Enantiomerically pure(R) and (S)- binol (Aldrich) was used as received. Compounds (**5.26**)[38] and (**5.27**)[39] and were prepared exactly as described in the literature.

Enantiomerically pure **5.25** was synthesized in the same manner as described for the racemic.

Preparation of Samples for Circular Dichroism

A solution of 4mg of mesoporous silica was combined with 4 mL of EtOH in a clean vial. The sample was sonicated at room temperature for 30 seconds. The solution was transferred by pipette to a quartz cuvette (pathlength 1cm) and the spectrum obtained using a JASCO J-715 spectrometer.

Preparation of Samples for Transmission Electron Microscopy

A small amount of sample was placed in a glass vial and ~50mL of ethanol was added. The solution was sonicated for 15 minutes. 20 mL of the solution was removed using a micropipette and dropped onto a carbon coated 200 mesh copper EM grid. The grid was left to dry overnight. The sample was examined using a JEOL 200keV STEM. Images were collected on a 4x4k Gatan digital camera, using Digital Micrograph to acquire and analyse the data.

Preparation of Samples for physical adsorption

Analysis was carried out with a Micromeritics ASAP 2010 (Accelerated Surface Area and Porosimetry System). Approximately 80-100 mg of material was carefully loaded into the tube which was then evacuated and backfilled with nitrogen. The mass was then accurately measured 4 times and averaged. The sample was then analyzed using standard methods.

Synthesis of 2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl-bis(triethoxysilane) 5.25

To a dry argon filled 25 mL schlenk tube containing a Teflon coated stir bar, was added 3,3'-diiodo-2,2'-dimethoxy-1,1'-binaphthyl (847 mg, 2 mmol) and chloro(1,5-cyclooctadiene)rhodium (I) dimer (74 mg, 0.15 mmol) under an inert atmosphere of nitrogen. The flask was then capped and sealed with Teflon tape, evacuated and backfilled with argon 3 times. The flask was then charged with dry degassed DMF (4 mL) followed by freshly distilled NEt_3 (1.2 ml, 9 mmol) and the resulting mixture was stirred at rt for 10 mins. Through the schlenk valve, triethoxysilane was added dropwise (1.1 ml, 6 mmol) at 0^{o}C. The schlenk valve was then closed under argon, stirred at rt for 2h then 80^{o}C and monitored by TLC. After 6 hours, the flask was allowed to cool to room temperature and the mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (1.5 mL) and purified over silica gel column using a gradient elution of 12%-20% THF:Hexanes. Pure fractions were collected, while mixed fractions were subjected to preparatory TLC developed at 12% THF/Hexanes, to afford the product **5.25** (454mg, 0.71mmol, 47%) as a clear viscous oil. IR (film CH_2Cl_2)(ν_{max} 2976, 2252, 1099, 907, 732, cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3) δ ppm 8.42 (s, 2H), 8.03 (d, *J* = 8.07 Hz, 2H), 7.45 (ddd, *J* = 8.09, 6.83, 1.16 Hz, 2H), 7.35 (ddd, *J* = 8.22, 6.80, 1.33 Hz, 2H), 7.16 (d, *J* = 8.48 Hz, 2H), 3.97 (q, *J* = 7.0 Hz, 6H), 3.28 (s, 3H), 1.25 (t, *J* =7.7 Hz, 18H). ^{13}C NMR (101 MHz, CD_3COCD_3) δ ppm 162.4 (2C), 141.2 (2C), 137.9 (2C), 132.2 (2C), 130.6 (2C), 129.2 (2C), 128.2 (2C), 127.2 (2C), 126.5 (2C), 124.6 (2C), 61.9 (2C), 60.4 (6C), 19.8 (6C). LRMS (EI) m/z (rel intensity) 638 (100) HRMS calcd for $C_{34}H_{46}O_8Si_2$: 638.2731, found TOF MS EI+ 638.2748.

Preparation of MAT 1 –15 Wt% R/S (5.25) – Brij 76/ HCl

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer). Brij-76 (0.467 g), DI H_2O (13.697 g) and 37% HCl (1.011 g) were stirred together at 60 ^oC for 1 h. NaCl (1.318 g) was then added and the resulting mixture was stirred (speed 4) at 60^oC for an additional 3 h. EtOH (1.186 g), 4,4'-bistriethoxysilyl)biphenyl (629 mg) and (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (126 mg) were premixed and added at 60^oC. The vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80^oC for 24h. Solids were recovered by filtration and washed with 400 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl, 72 h. After 24 h under vacuum at room temperature, 0.451g of a fine colourless powder was recovered.

Preparation of Mat 2- 15 Wt% R/S (5.25) – C_{18}TABr/ NaOH

In a 30ml jar containing a new l182 Teflon coated stir bar (Fischer), NaOH (0.3366 g), DI H_2O (17.955g) and 0.5247 g of C_{18}TABr were stirred for 30 min at 50^oC. To this solution at room temperature was added 423 mg bistriethoxysilyl)biphenyl, 82.2 mg (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) and 0.4866g anhydrous ethanol. The mixture was stirred (speed 4) at room temperature for 20h and left to age statically at 95°C for 20h. Solids were recovered by filtration, and washed with 400 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a

solution of 200 mL ethanol and 2 mL 37% HCl for 72 h. After 24 h under vacuum at room temperature, 0.273 g of a colourless powder was recovered.

Preparation of MAT 3- 15 Wt% R/S (5.25) – P123/ HCl

In a 30ml jar containing an l182 Teflon coated stir bar. P123 0.5602 g, DI H2O 19.939 g, and 0.153 g HCl, were stirred in a closed bottle overnight. To this solution at room temperature was added 469 mg bistriethoxysilyl)biphenyl, 90 mg (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) and 0.600 g of anhydrous ethanol at 0^{o}C. The mixture was stirred (speed 4) at 0^{o}C for 1h and then warmed to 40^{o}C and the resulting mixture was stirred for 24 h. Static aging was carried out at 100^{o}C for 24h. Upon aging, the solids were observed to aggregate and form a solid gel. Solids were recovered by filtration, broken up with a spatula and washed with 400 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h. After 24 h under vacuum at room temperature, 0.254 g was recovered.

Preparation of MAT 4 - 15Wt% R/S (5.25) – F127/ HCl

In a 30ml jar containing an l182 Teflon coated stir bar, F127 0.5602 g, DI H2O 19.939 g, and 0.153 g HCl, were stirred overnight. To this solution at room temperature was added 469 mg bistriethoxysilyl)biphenyl, 90 mg (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) mixed with 600 anhydrous ethanol at 0^{o}C. The mixture was stirred (speed 4) at 0^{o}C 1h then warmed to 40^{o}C and the resulting mixture was stirred for

24 h and aged statically at 100°C 24h. Solids were recovered by filtration, and washed with 400 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h. After 24 h under vacuum at room temperature, 0.032 g was recovered which was insufficient for analysis.

Preparation of MAT 5- 5 Wt% S (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), BriJ76 (0.233 g), DI H_2O (6.848 g) and 37% HCl (505 g) were stirred together at 60 °C for 1 h. NaCl (0.659 g) was then added and the resulting mixture was stirred (speed 4) at 60°C for an additional 3 h. EtOH (0.593g), 4,4'-bistriethoxysilyl)biphenyl (300 mg), (S) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (15.6mg) were premixed an added at 60°C, the vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80°C for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.168 g of a fine colourless powder was recovered.

Preparation of MAT 6- 5 Wt% R (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), BriJ76 (0.233 g), DI H_2O (6.848 g) and 37% HCl (505 g) were stirred together at 60 °C for 1 h. NaCl (0.659 g) was then added and the resulting mixture was stirred (speed 4) at 60°C for

an additional 3 h. EtOH (0.593g), 4,4'-bistriethoxysilyl)biphenyl (460 mg), (R) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (27.6 mg) were premixed and added at 60°C, the vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80°C for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.231 g of a fine colourless powder was recovered.

Preparation of MAT7- 15 Wt% S (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.233 g), DI H_2O (6.848 g) and 37% HCl (505 g) were stirred together at 60 °C for 1 h. NaCl (0.659 g) was then added and the resulting mixture was stirred (speed 4) at 60°C for an additional 3 h. EtOH (0.593g), 4,4'-bistriethoxysilyl)biphenyl (314 mg), (S) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (64.8 mg) were premixed an added at 60°C, the vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80°C for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.193 g of a fine colourless powder was recovered.

Preparation of MAT8- Wt% 15% S (5.25) –Treated Hydrothermally

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.233 g), DI H_2O (6.848 g) and 37% HCl (505 g) were stirred together at 60 ^oC for 1 h. NaCl (0.659 g) was then added and the resulting mixture was stirred (speed 4) at 60^oC for an additional 3 h. EtOH (0.593g), 4,4'-bistriethoxysilyl)biphenyl (314 mg), (*S*) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (64.4 mg) were premixed an added at 60^oC, the vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80^oC for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. The recovered material was then placed in a new 4 DR vial (VWR) with 8 g DI H_2O and heated to 100^oC for 4 h, after cooling to room temperature the solids were filtered and extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.193 g of a fine colourless powder was recovered.

Preparation of MAT9- 15 Wt% R (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.233 g), DI H_2O (6.848 g) and 37% HCl (505 g) were stirred together at 60 ^oC for 1 h. NaCl (0.659 g) was then added and the resulting mixture was stirred (speed 4) at 60^oC for an additional 3 h. EtOH (0.593g), 4,4'-bistriethoxysilyl)biphenyl (314 mg), (R) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (64.8 mg) were premixed an added at 60^oC, the vial was capped and the resulting mixture was stirred for 20h (speed

4). The material was aged under static conditions at 80°C for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h. After 24 h under vacuum at room temperature, 0.187 g of a fine colourless powder was recovered.

Preparation of MAT10 - 15 Wt% R (5.25) –Treated Hydrothermally

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.233 g), DI H_2O (6.848 g) and 37% HCl (505 g) were stirred together at 60 °C for 1 h. NaCl (0.659 g) was then added and the resulting mixture was stirred (speed 4) at 60°C for an additional 3 h. EtOH (0.593g), 4,4'-bistriethoxysilyl)biphenyl (314 mg), (*R*) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (64.4 mg) were premixed an added at 60°C, the vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80°C for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. The recovered material was then placed in a new 4 DR vial (VWR) with 8 g DI H_2O and heated to 100°C for 4 h, after cooling to room temperature the solids were filtered and extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.182 g of a fine colourless powder was recovered.

Preparation of MAT11- 30Wt% S (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.233 g), DI H_2O (6.848 g) and 37% HCl (505 g) were stirred together at 60 ^oC for 1 h. NaCl (0.659 g) was then added and the resulting mixture was stirred (speed 4) at 60^oC for an additional 3 h. EtOH (0.593g), 4,4'-bistriethoxysilyl)biphenyl (200 mg), (*S*) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (85 mg) were premixed an added at 60^oC, the vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80^oC for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h. After 24 h under vacuum at room temperature, 0.179 g of a fine colourless powder was recovered.

Preparation of MAT12- 30Wt% R (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.233 g), DI H_2O (6.848 g) and 37% HCl (505 g) were stirred together at 60 ^oC for 1 h. NaCl (0.659 g) was then added and the resulting mixture was stirred (speed 4) at 60^oC for an additional 3 h. EtOH (0.593g), 4,4'-bistriethoxysilyl)biphenyl (266 mg), (R) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (114 mg) were premixed an added at 60^oC, the vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80^oC for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried

out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.215 g of a fine colourless powder was recovered.

Preparation of MAT13 - 100% S (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.467 g), DI H_2O (13.697 g) and 37% HCl (1.01 g) were stirred together at 60 ^oC for 1 h. NaCl (1.318 g) was then added and the resulting mixture was stirred (speed 4) at 60^oC for an additional 3 h. EtOH (1.186g), (S) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (645 mg) were premixed an added at 60^oC, the vial was capped and the resulting mixture was stirred for 20h (speed 4). The material was aged under static conditions at 80^oC for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.342g of a fine colourless powder was recovered.

Preparation of MAT14- 15Wt% S (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.467 g), DI H_2O (13.697 g) and 37% HCl (1.01 g) were stirred together at 60 ^oC for 1 h. NaCl (1.318 g) was then added and the resulting mixture was stirred (speed 4) at 60^oC for an additional 3 h. EtOH (1.186g) and TEOS (980 mg), (*S*) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) (173 mg) were premixed an added at 60^oC, the

vial was capped and the reaction mixture stirred for 20h (speed 4). The material was aged under static conditions at 80°C for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.355 g of a fine colourless powder was recovered.

Preparation of MAT15- Wt% 5 R (5.25)

In a new 4 Dr vial (VWR) containing a new l182 Teflon coated stir bar (Fischer), Brij-76 (0.233 g), DI H_2O (6.84 g) and 37% HCl (.505 g) were stirred together at 60 °C for 1 h. NaCl (659 g) was then added and the resulting mixture was stirred (speed 4) at 60°C for an additional 3 h. EtOH (0.593g) and TEOS (570 mg), (R) (2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyl)bis(triethoxysilane) 30 mg) were premixed an added at 60°C, the vial was capped and the resulting mixture stirred for 20h (speed 4). The material was aged under static conditions at 80°C for 24h. Solids were recovered by filtration and washed with 200 mL of DI water. Extraction of the solvent was carried out via a soxhlet extrator with a solution of 200 mL ethanol and 2 mL 37% HCl for 72 h After 24 h under vacuum at room temperature, 0.203 g of a fine colourless powder was recovered.

5.7 References

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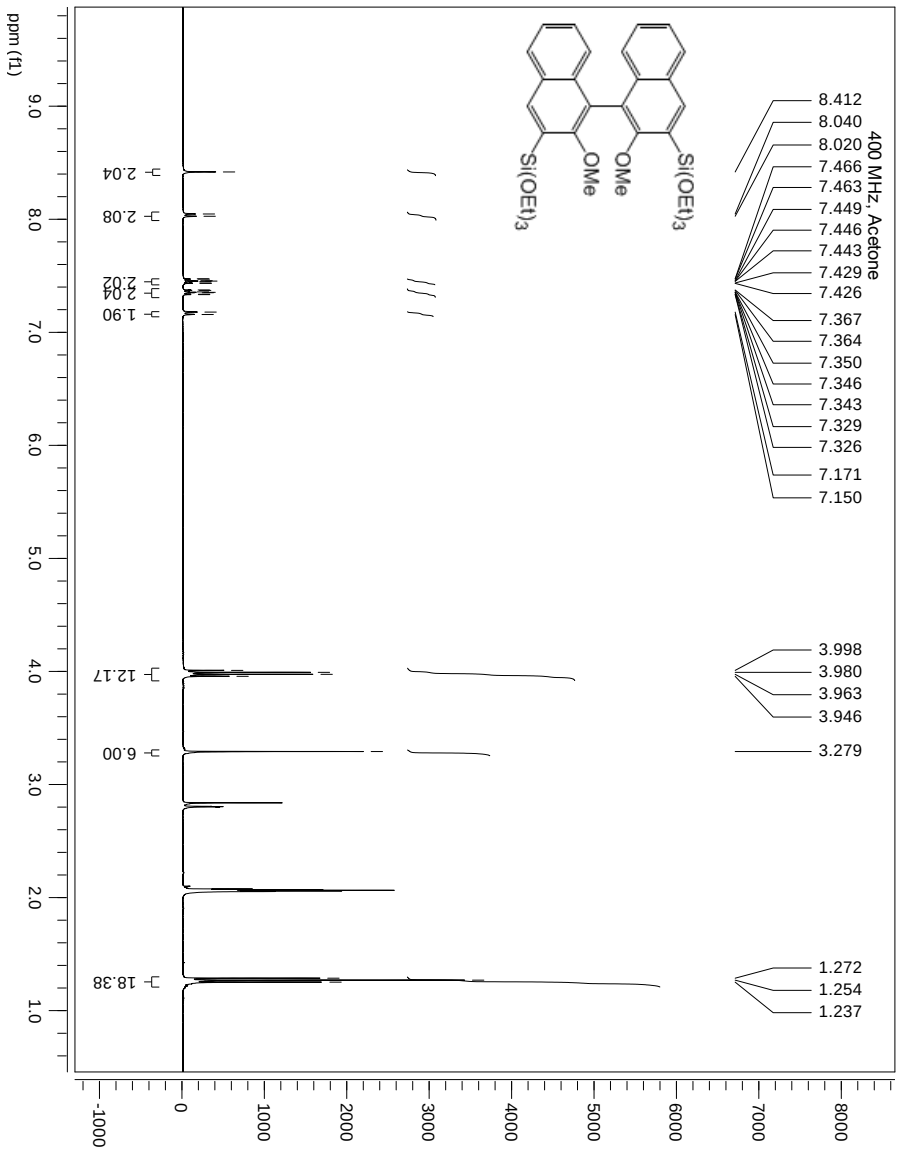
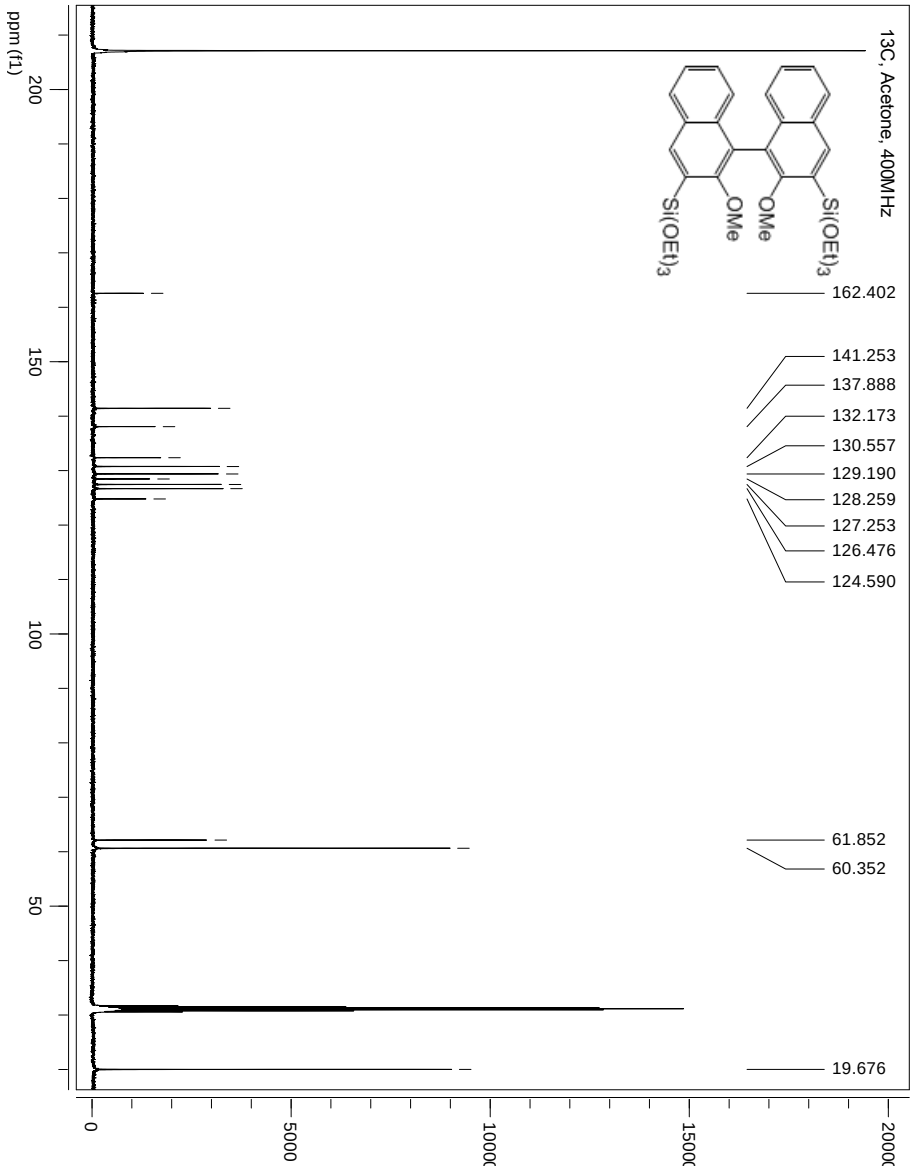
Appendix A

Data for Chapter 5

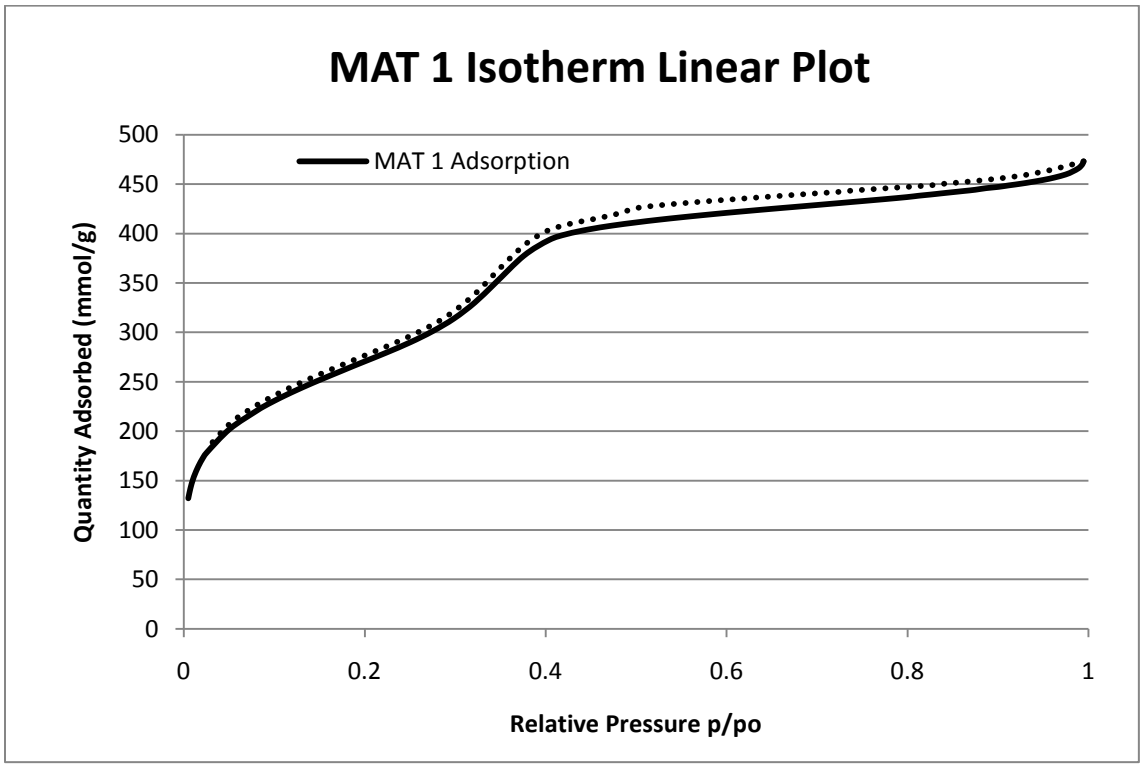
^{1}H NMR Spectrum of 5.25



^{13}C NMR spectrum of 5.25

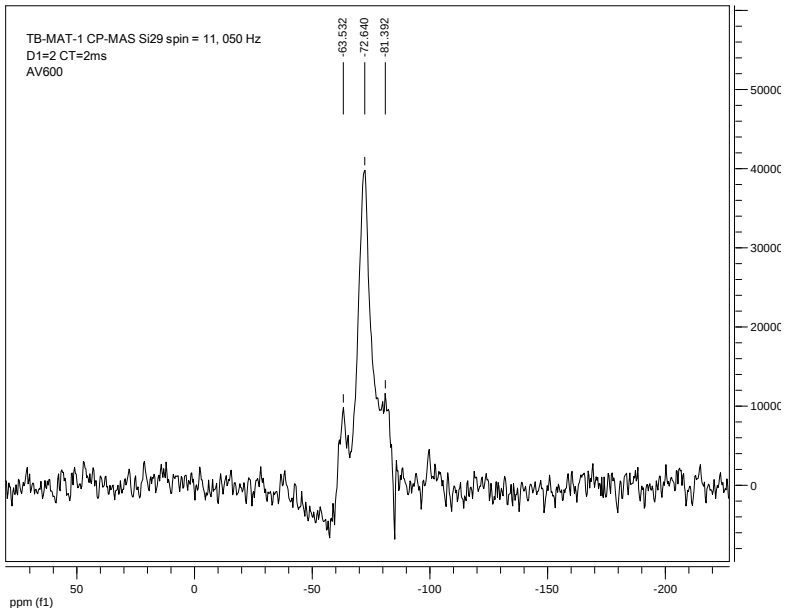


N_2 adsorption of MAT1 and summary of critical parameters

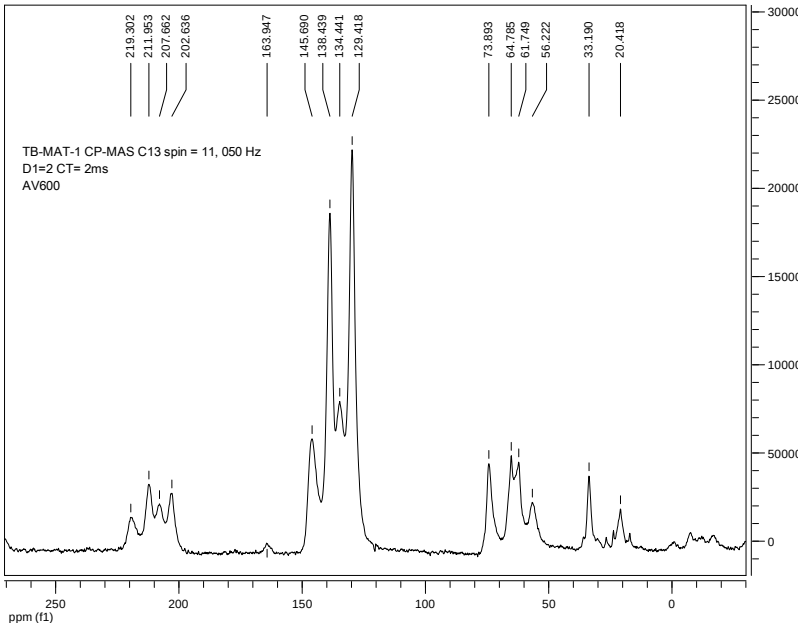


BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
22.7	978	0.676

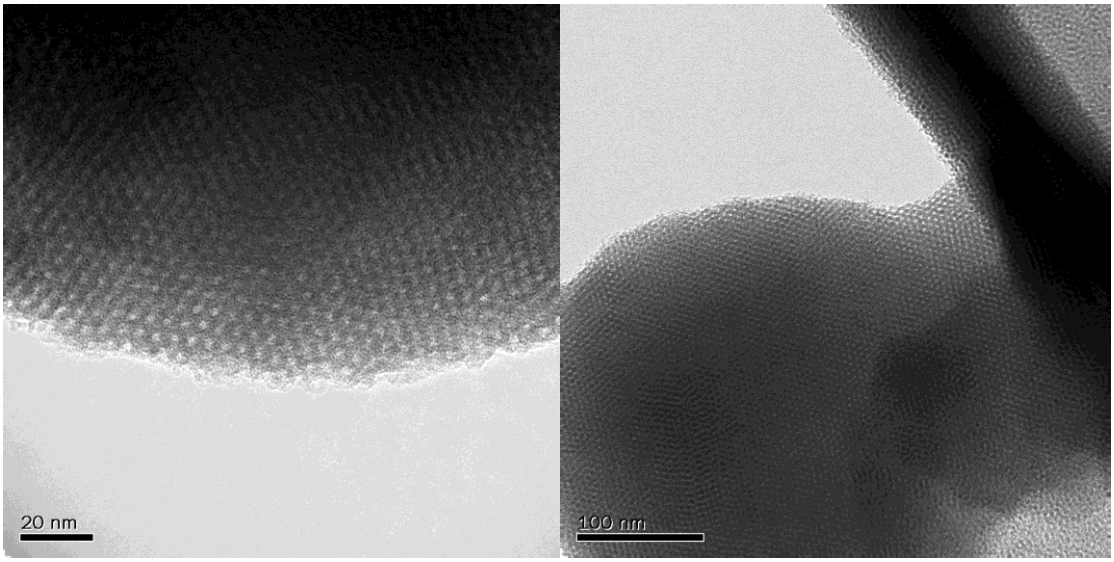
CP-MAS NMR ^{29}Si Mat 1

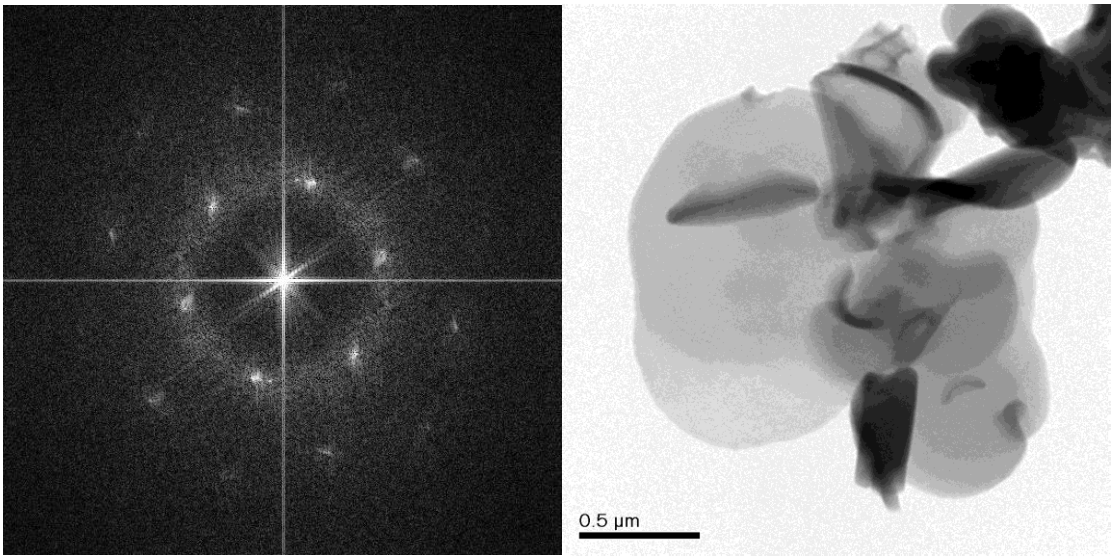


CP-MAS NMR ^{13}C Mat 1

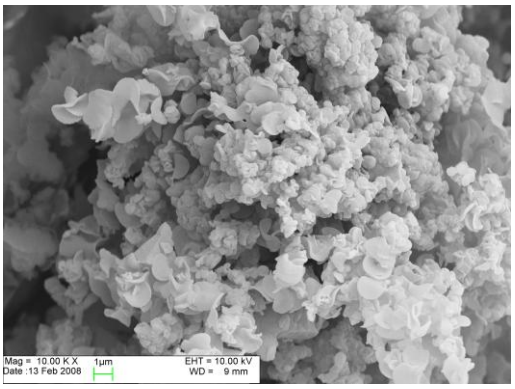


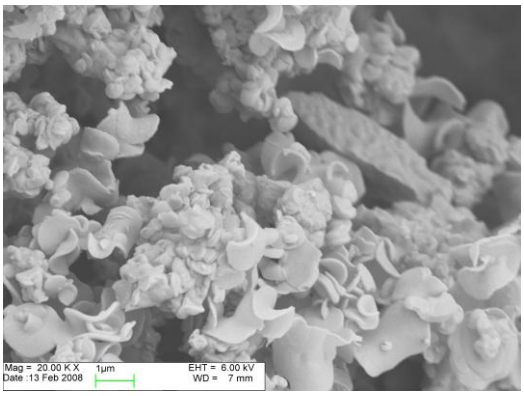
TEM Images of MAT 1

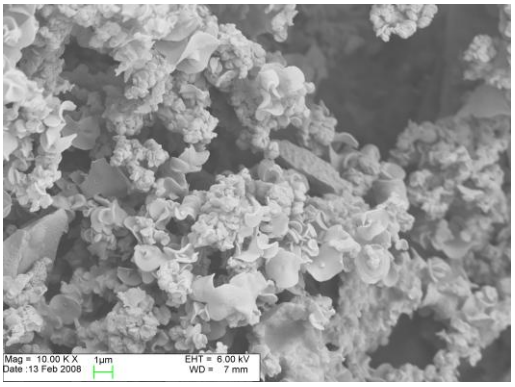


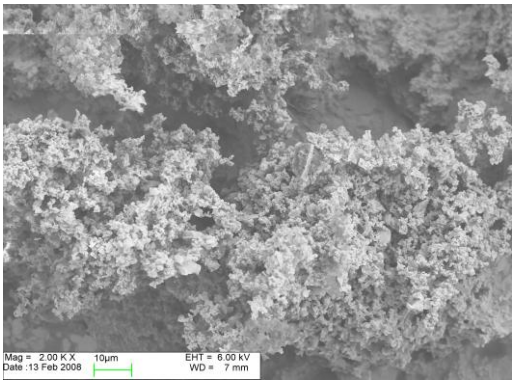


SEM Images of MAT1

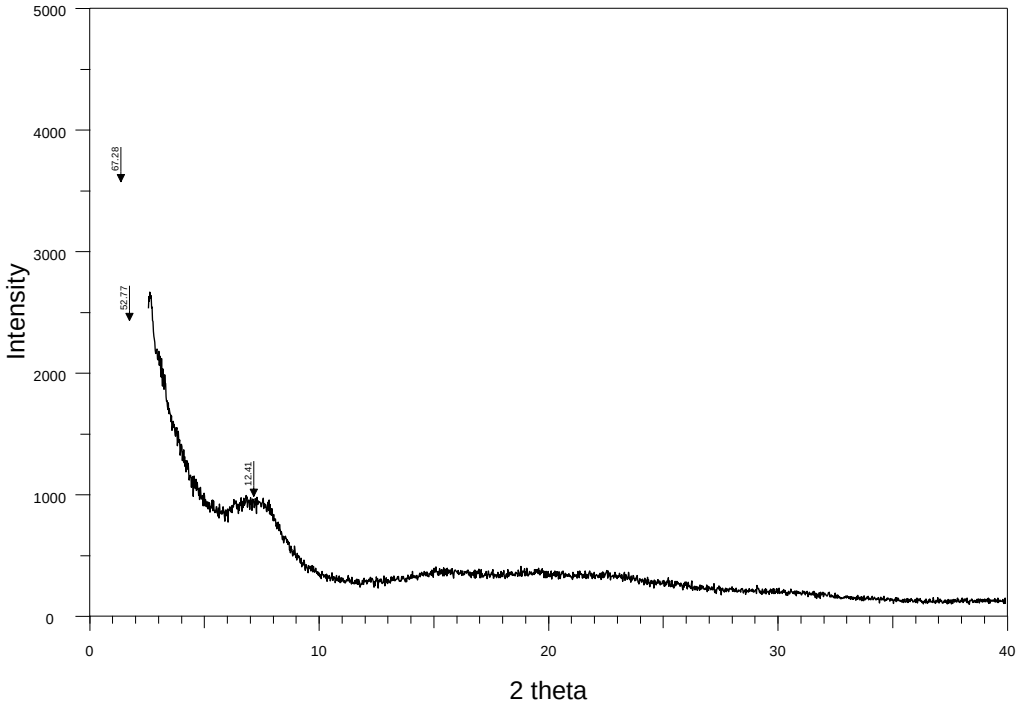






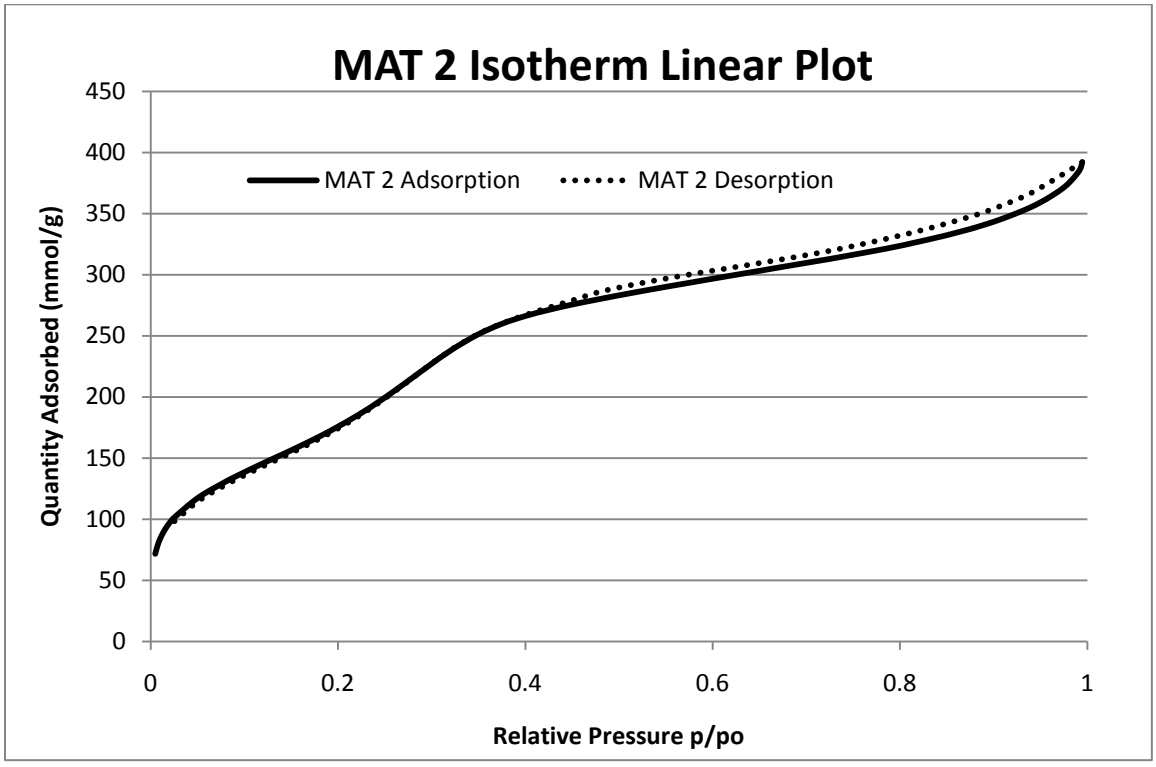


Powder X-ray pattern of samples MAT1



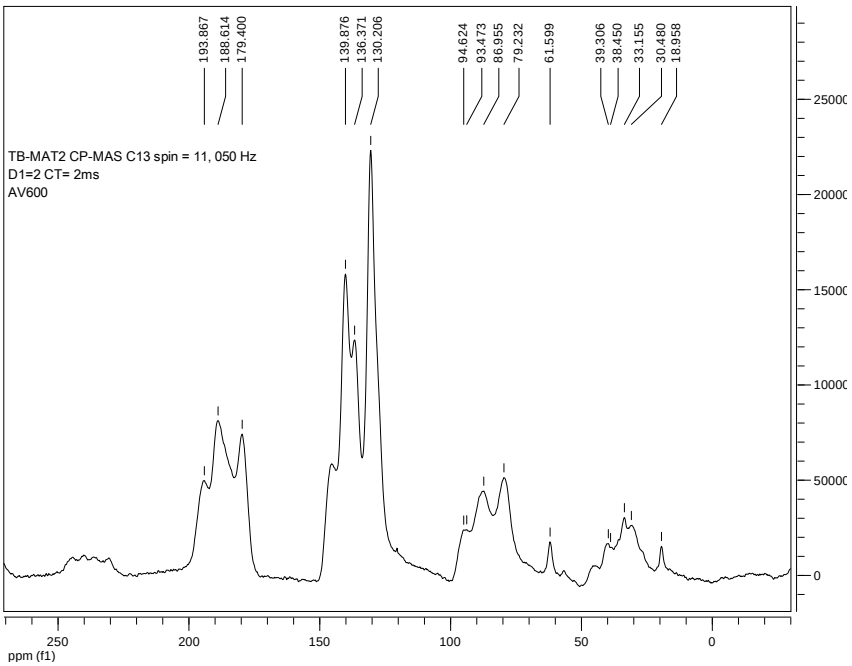
This sample has a mesostructure with d = 55-60Å. The bulk material is amorphous.

N_2 adsorption of MAT1 and summary of critical parameters

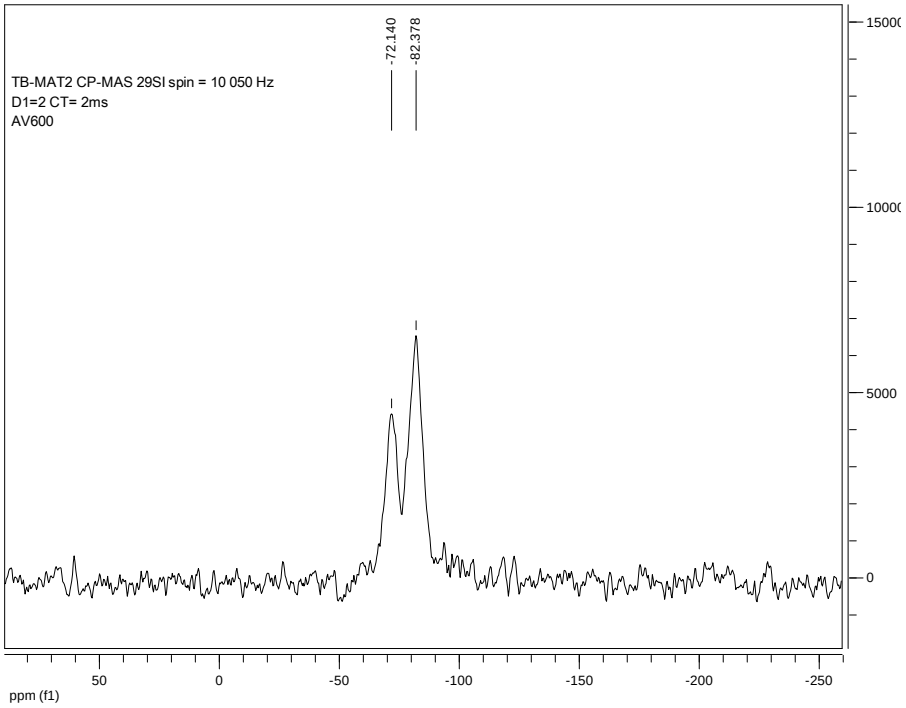


BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
27.8	669	0.565

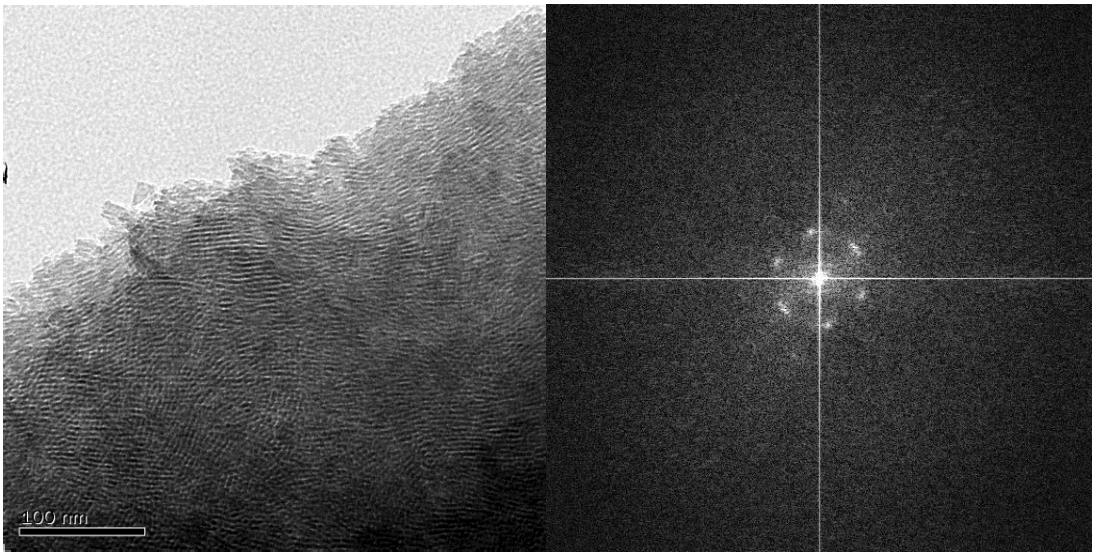
CP-MAS NMR ^{13}C MAT2

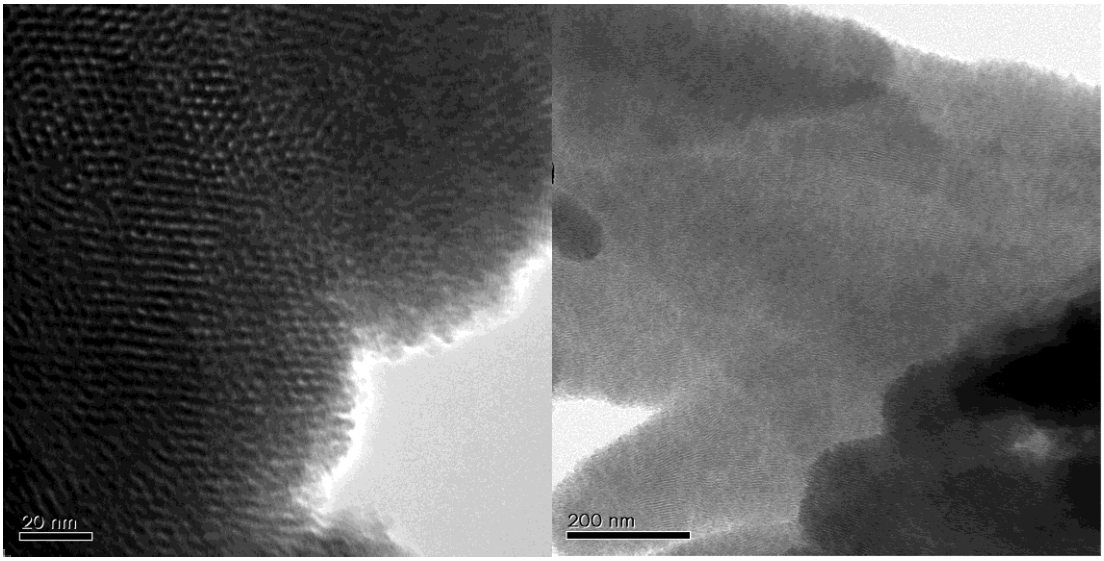


CP-MAS NMR ^{29}Si Mat 2

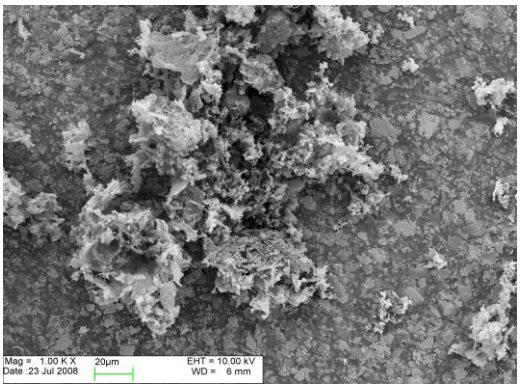


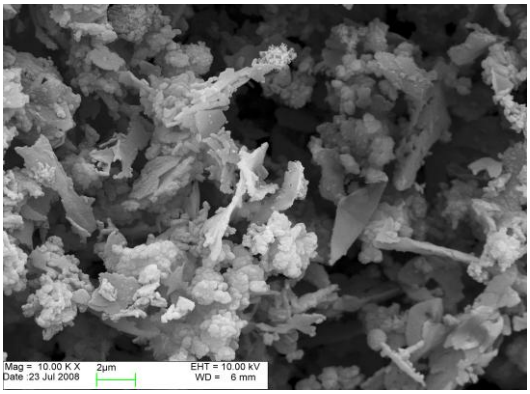
TEM Images of MAT 2

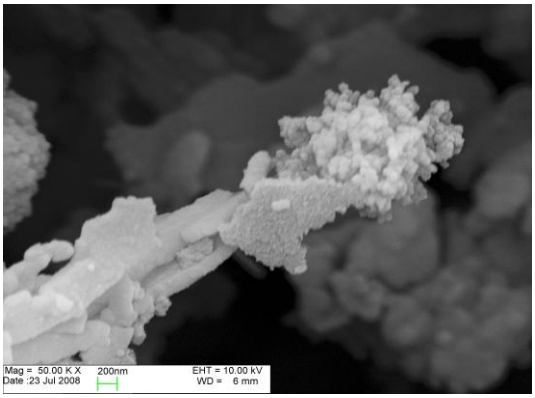


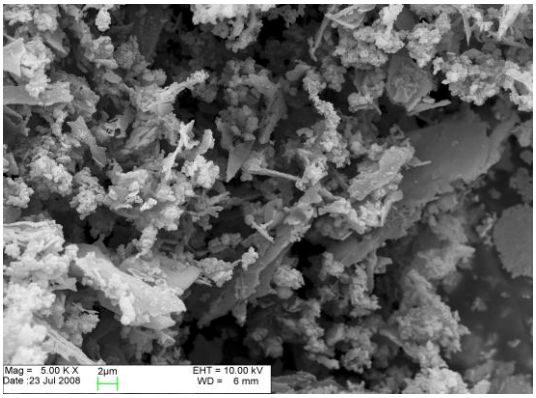


SEM Images of MAT 2

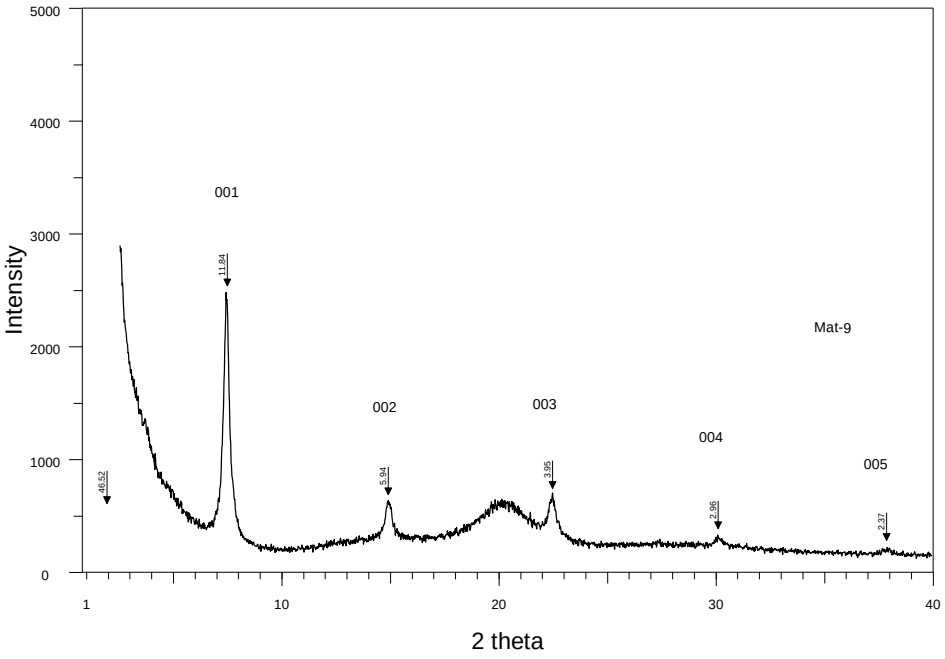






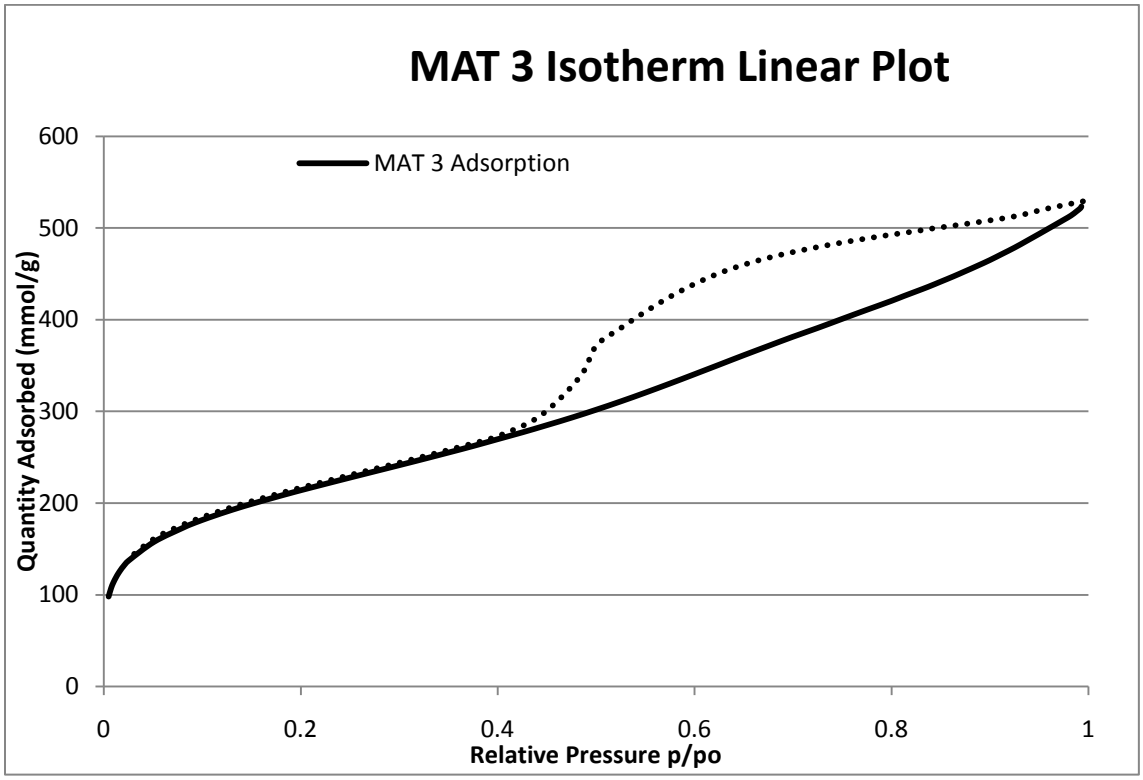


Powder X-ray pattern of samples MAT2.



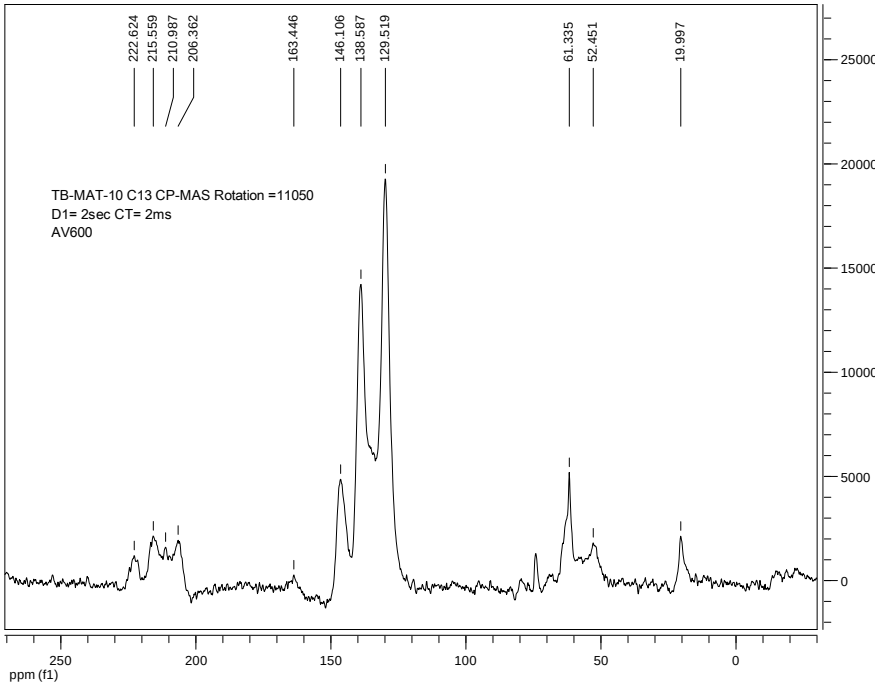
This sample possesses a poorly crystalline meso-structure with d = 47 Å. The rest of the sample has a layered structure with interlayer space of 11.8 Å.

N_2 adsorption of MAT3 and summary of critical parameters

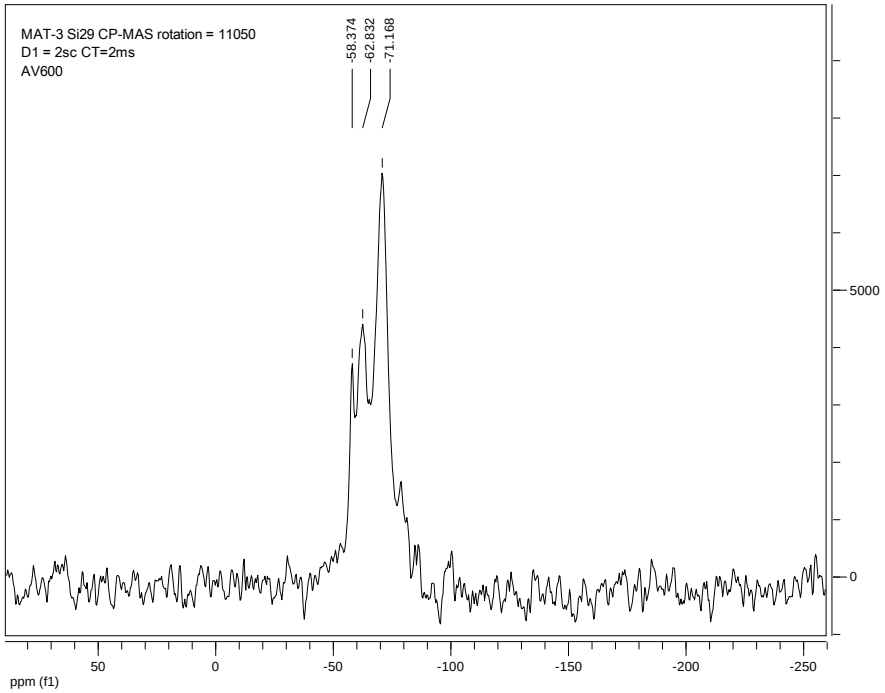


BJH Pore Diameter Å[a]	Surface Area m2/g	Pore Volume cm^3/g
36.6	669	0.725

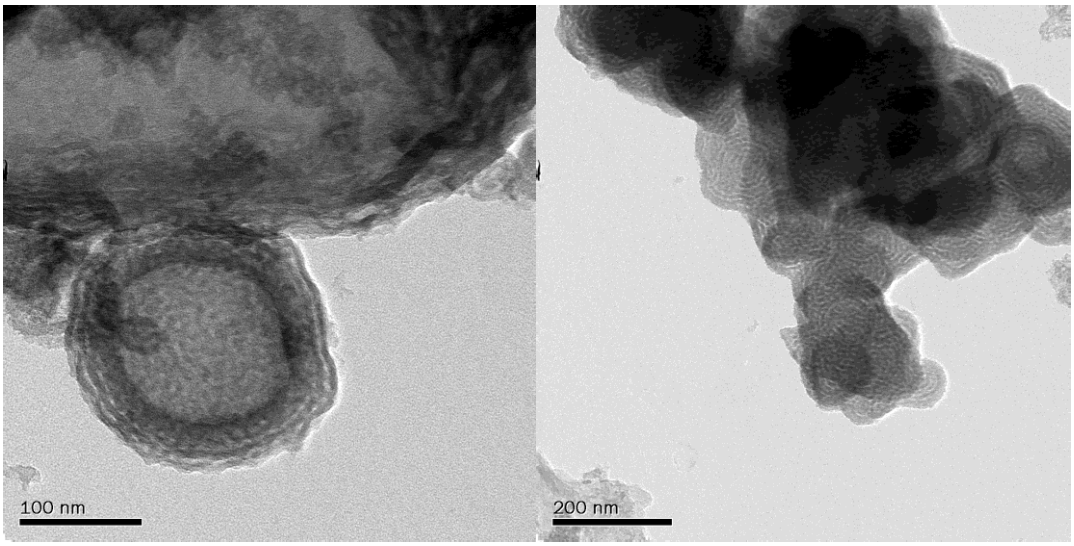
CP-MAS NMR ^{13}C MAT 3

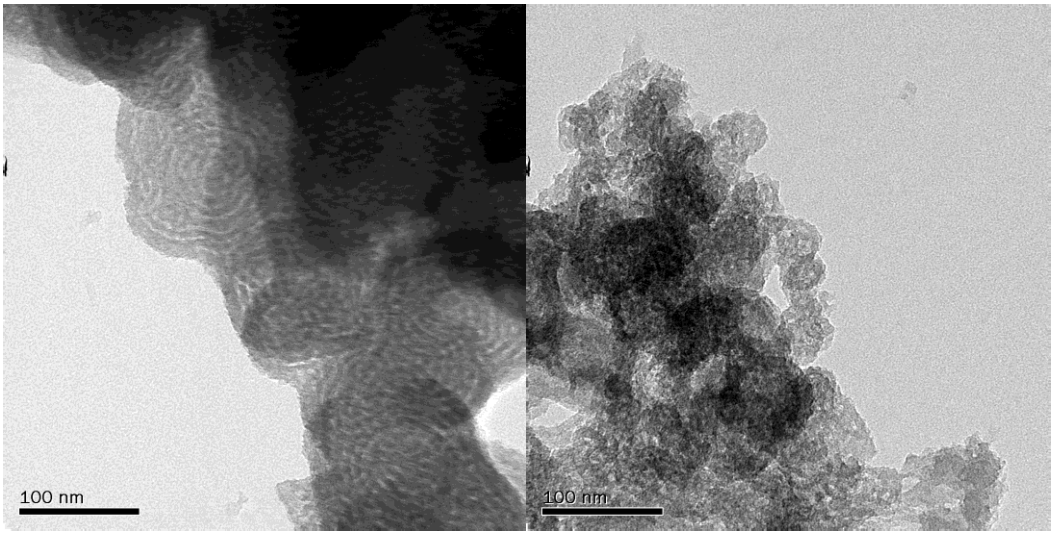


CP-MAS NMR ^{29}Si Mat 3

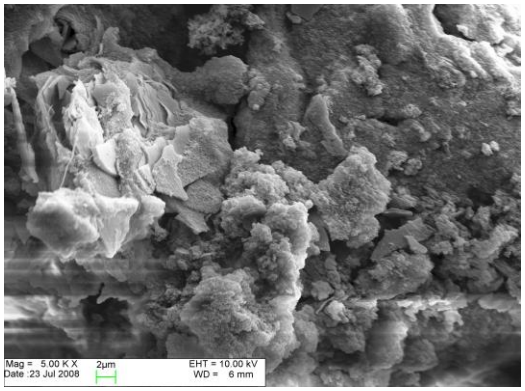


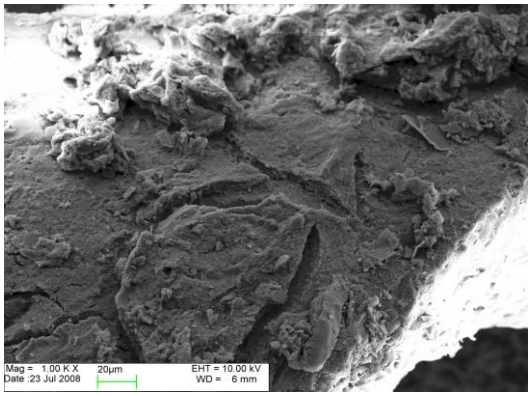
TEM Images of MAT3

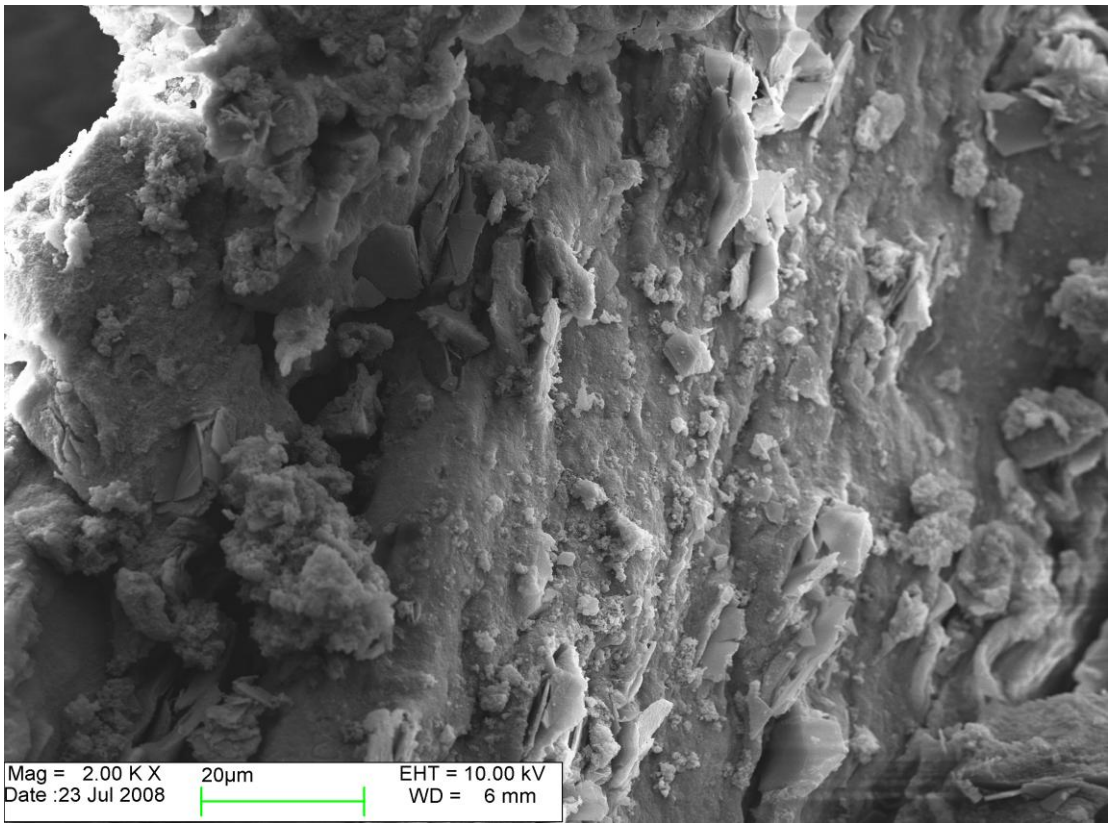




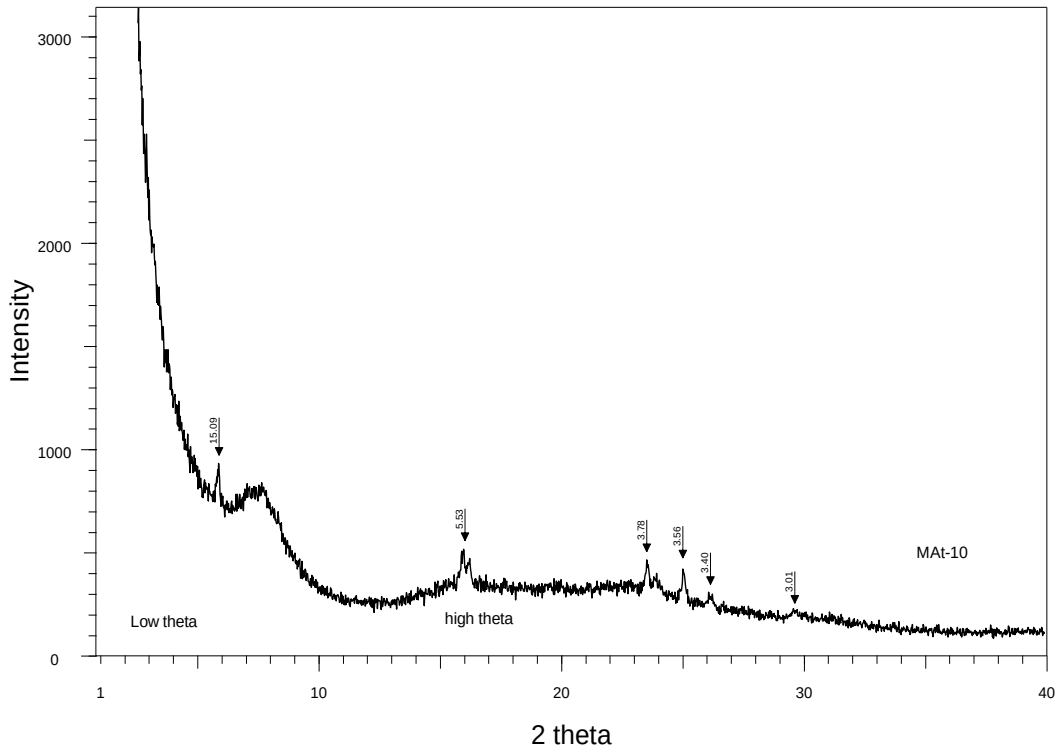
SEM Images of MAT3





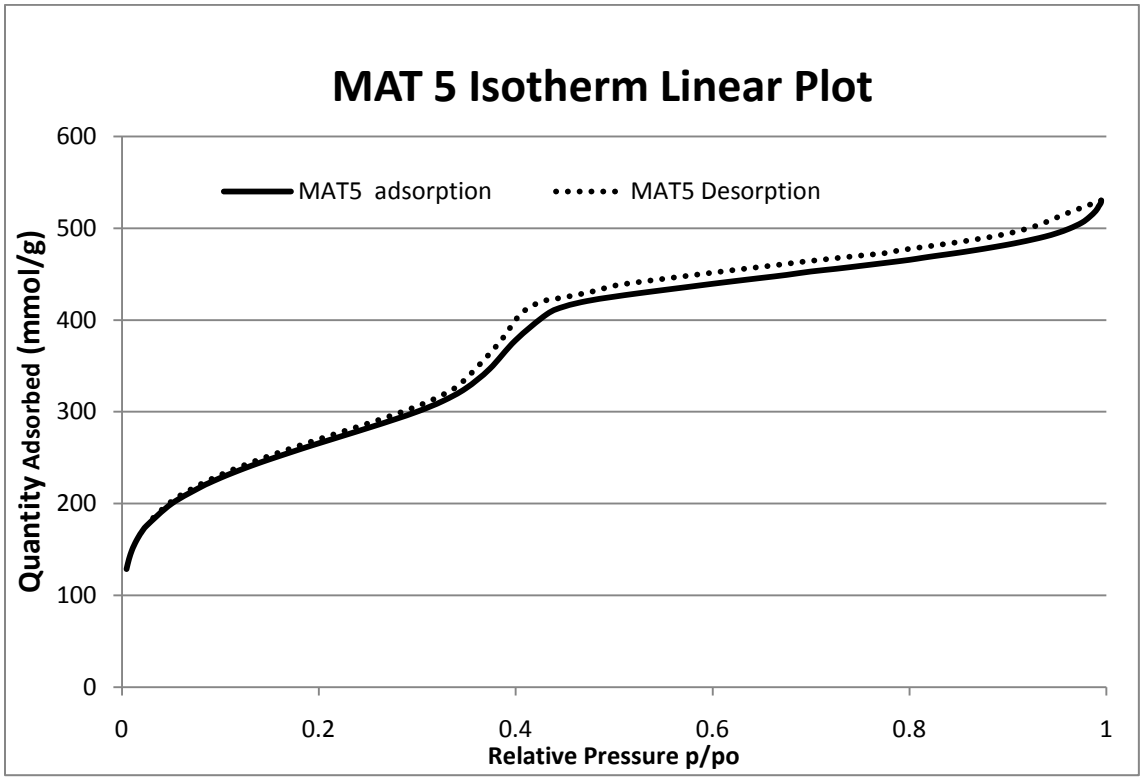


Powder X-ray pattern of samples MAT3.



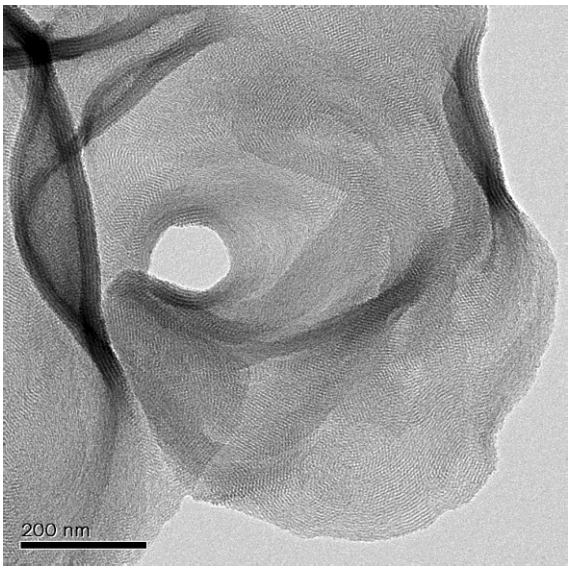
This sample does not have crystalline meso-structure. The rest of the sample is a mixture of amorphous and crystalline phases. The composition of the crystalline phase cannot be identified.

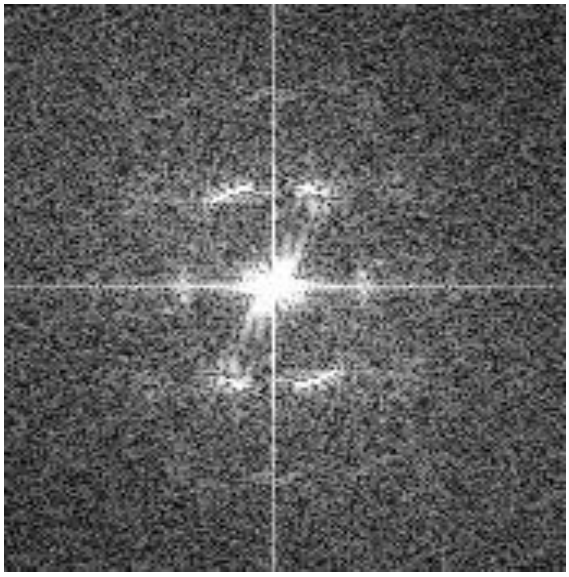
N_2 adsorption of MAT5 and summary of critical parameters

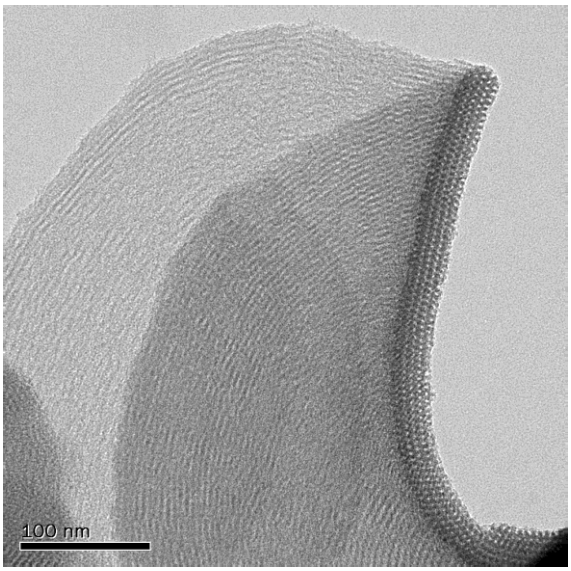


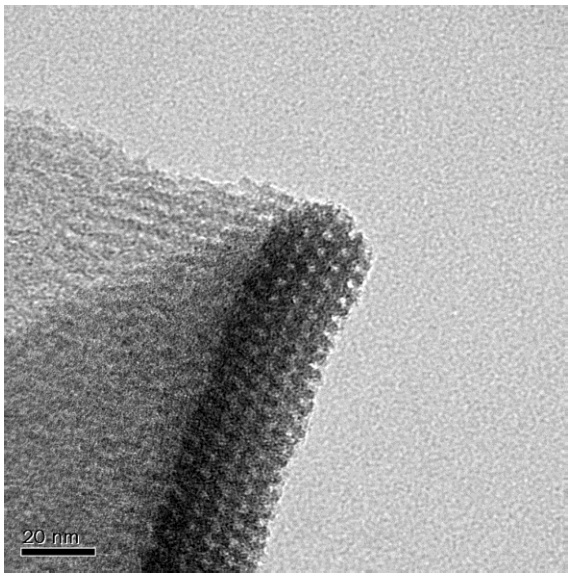
BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
26.9	957	0.760

TEM Images of MAT 5

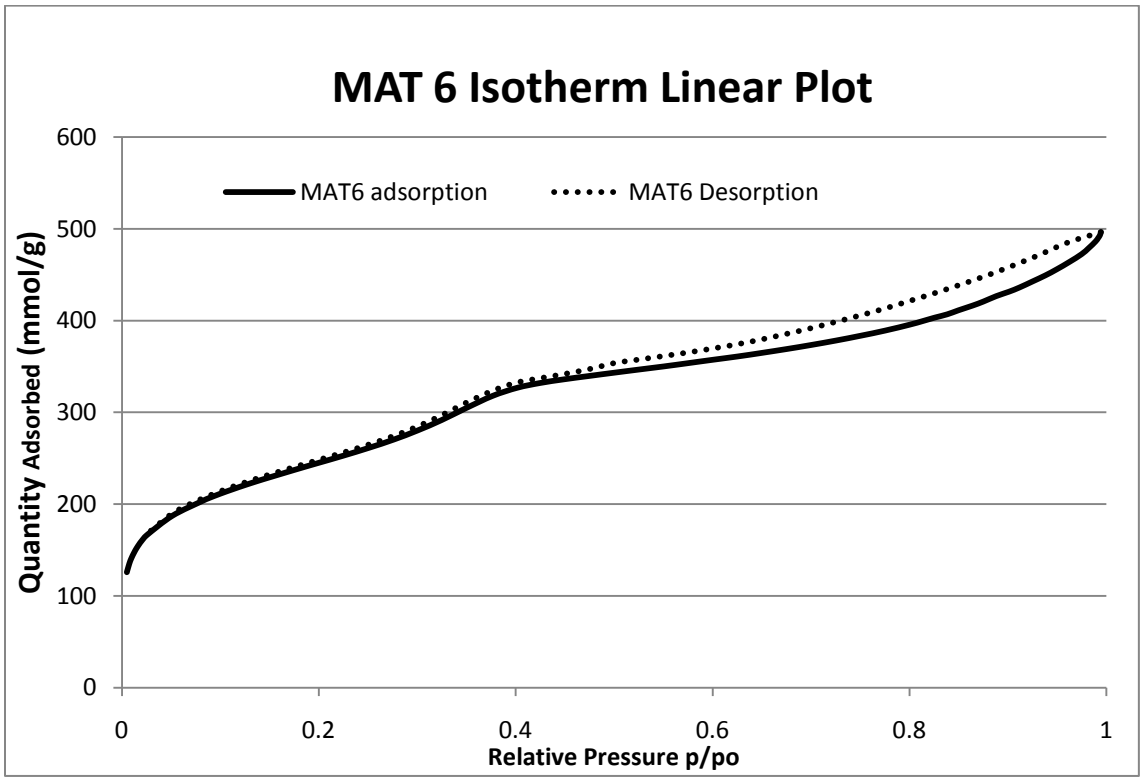






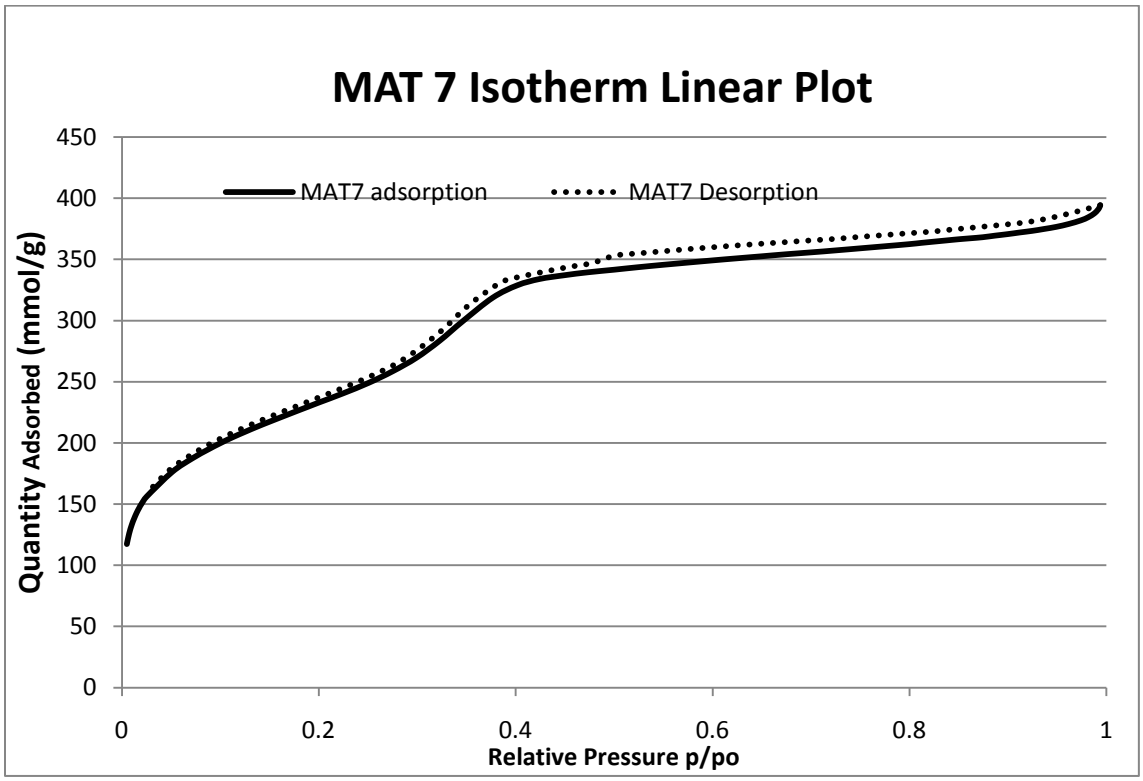


N_2 adsorption of MAT6 and summary of critical parameters



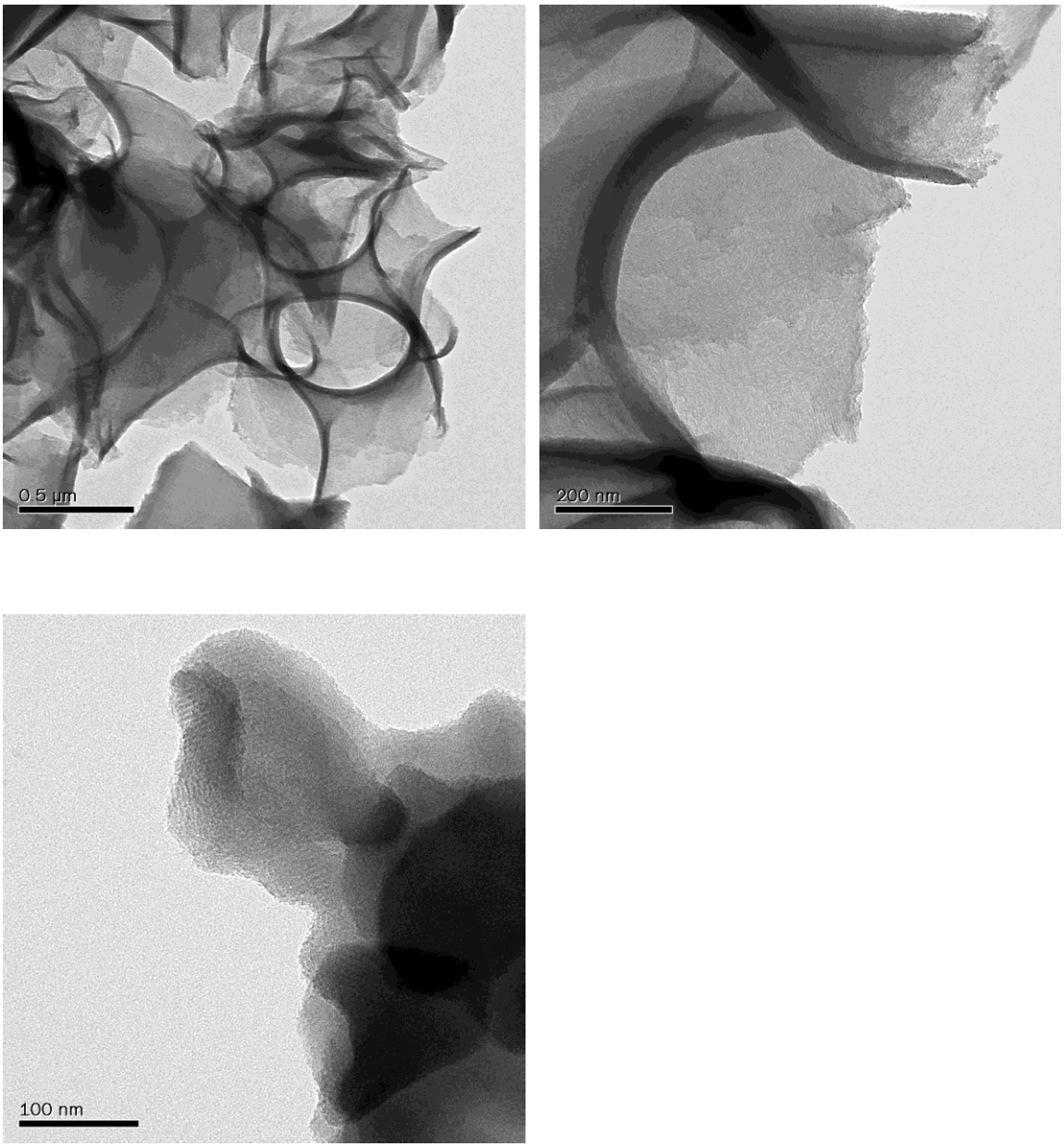
BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
27.9	878	0.711

N_2 adsorption of MAT7 and summary of critical parameters

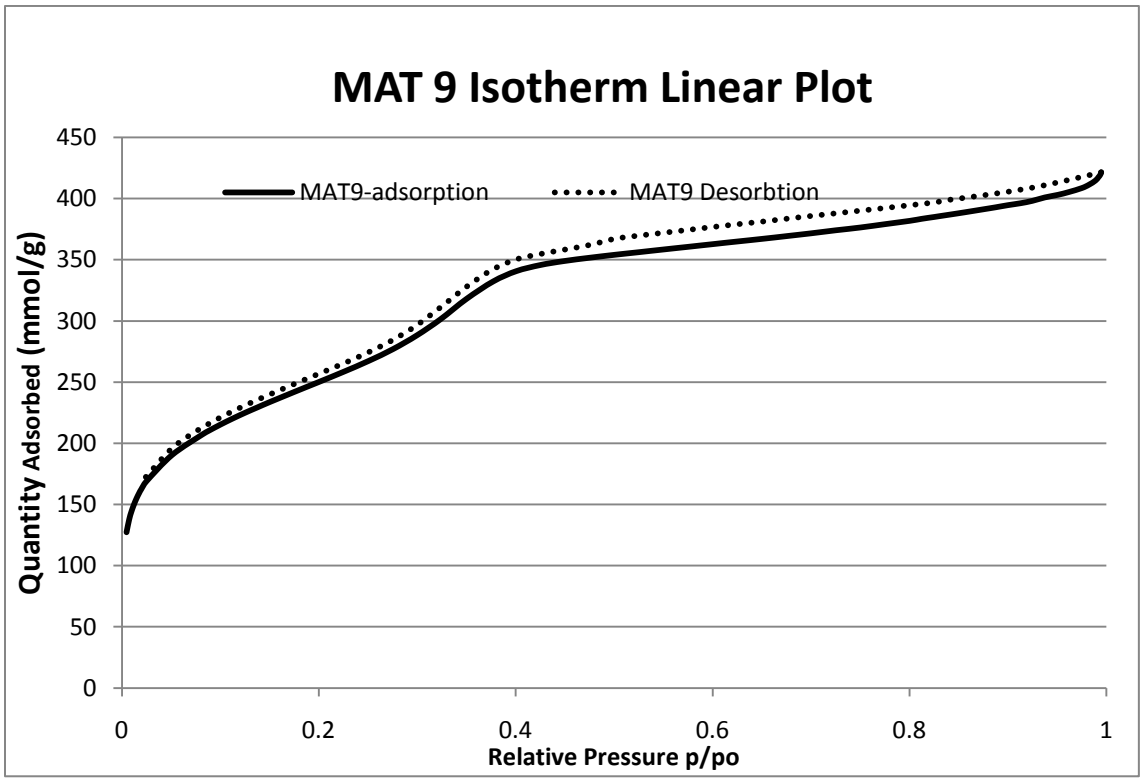


BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
22.6	838	0.563

Figure S 1 TEM Images of MAT 7

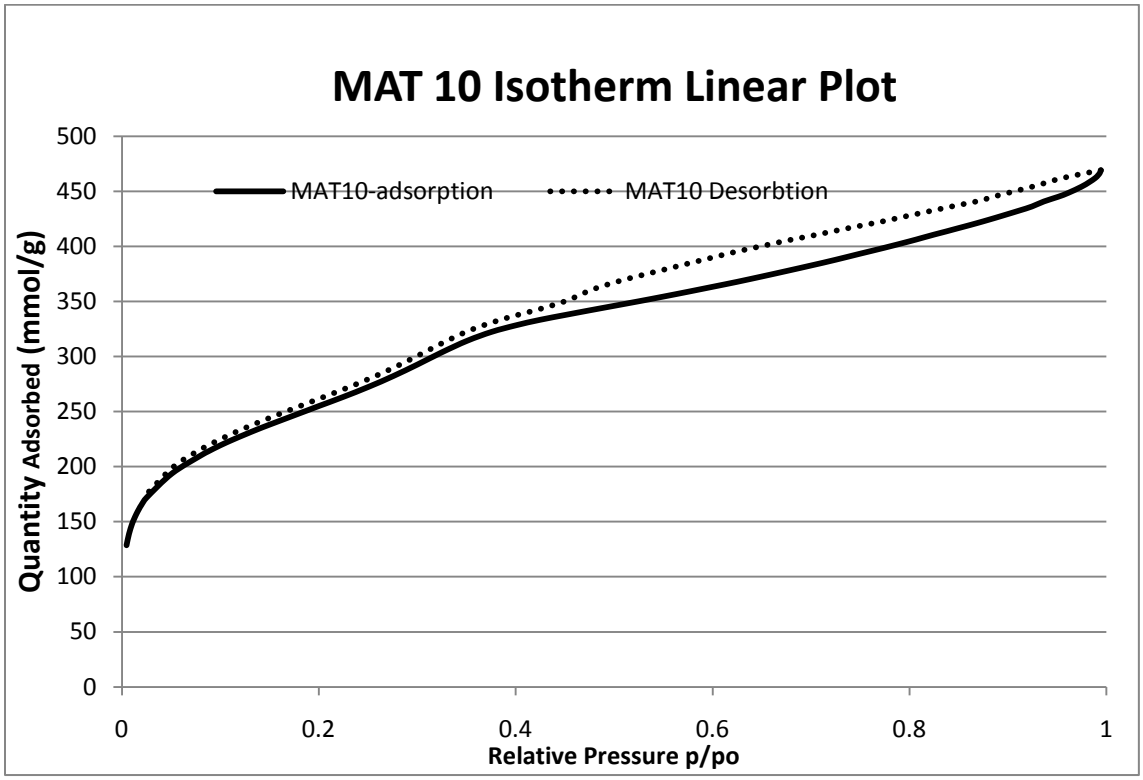


N_2 adsorption of MAT9 and summary of critical parameters



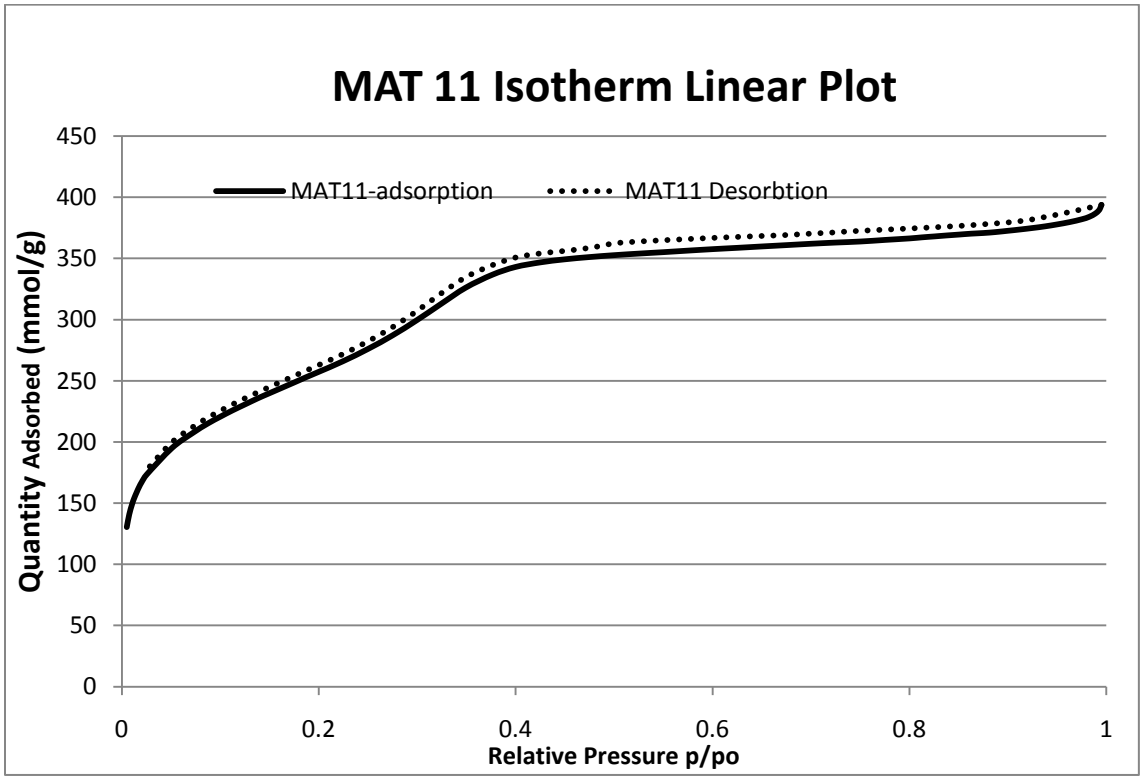
BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
22.8	871	0.596

N_2 adsorption of MAT10 and summary of critical parameters



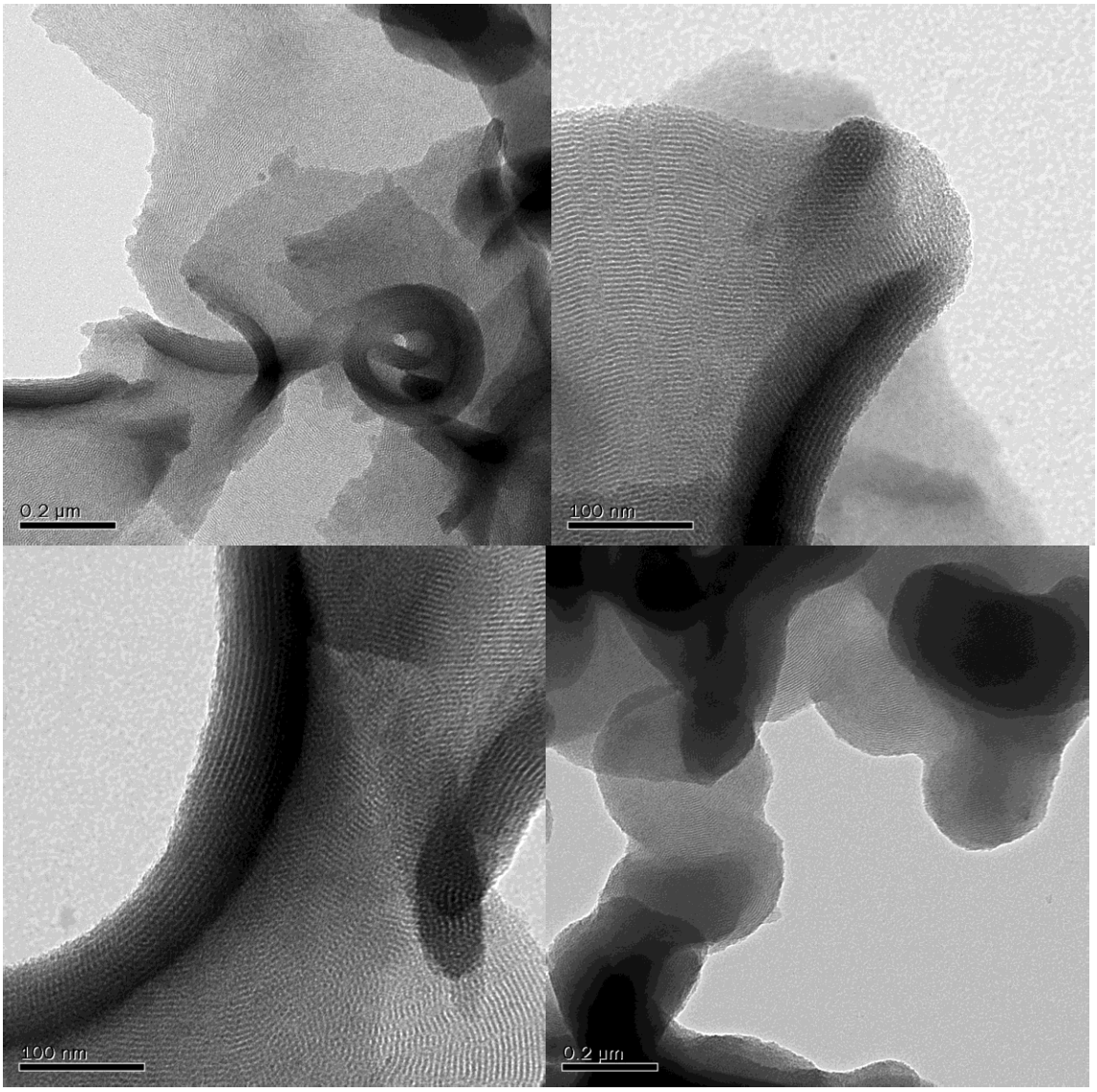
BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
25.3	916	0.665

N_2 adsorption of MAT11 and summary of critical parameters

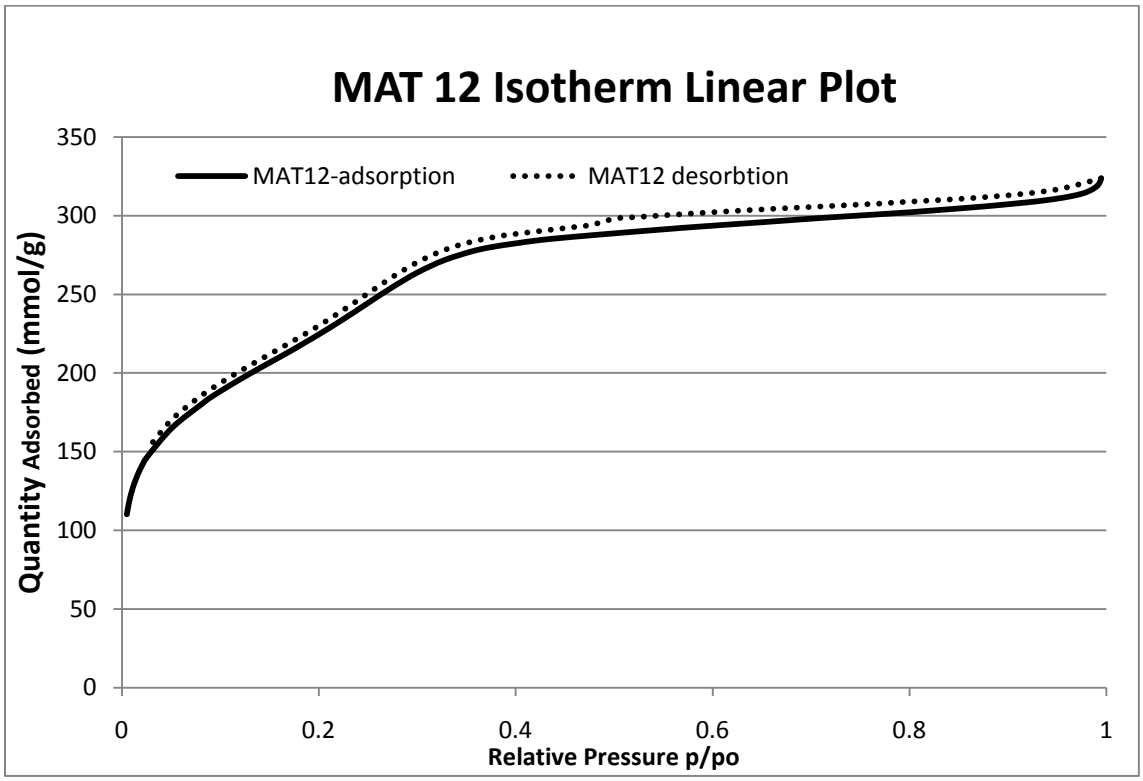


BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
20.6	926	0.548

TEM Images of MAT 11

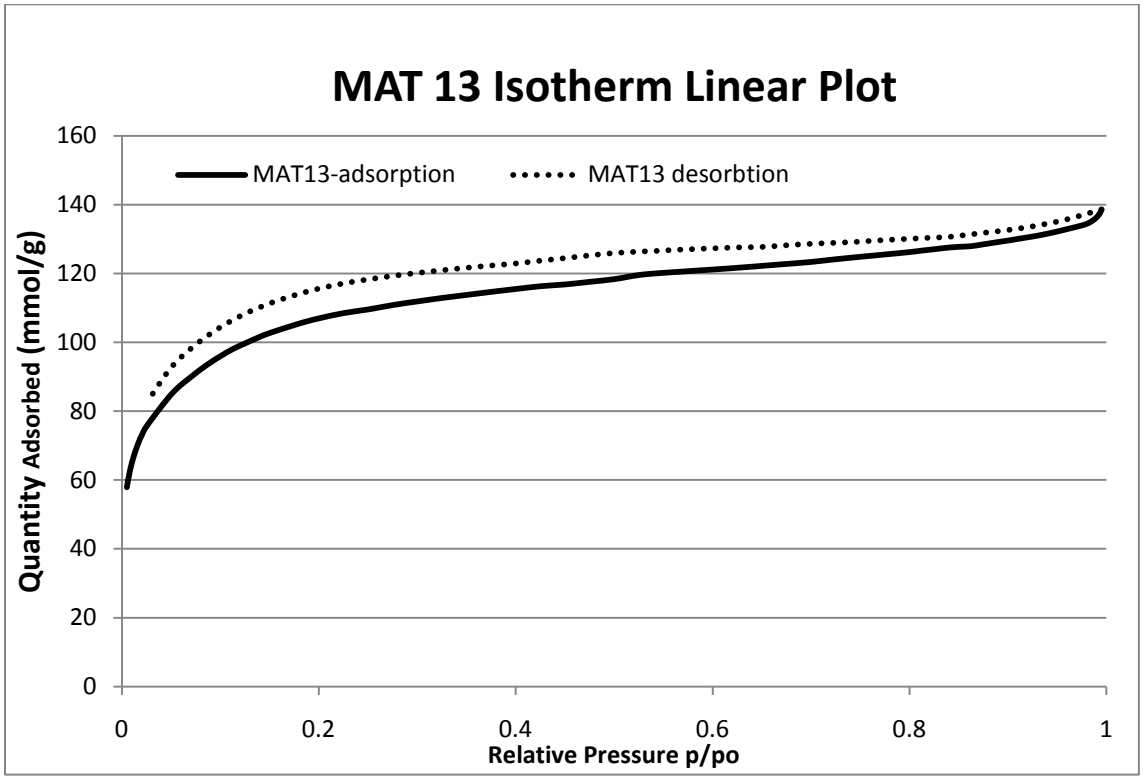


N_2 adsorption of MAT12 and summary of critical parameters



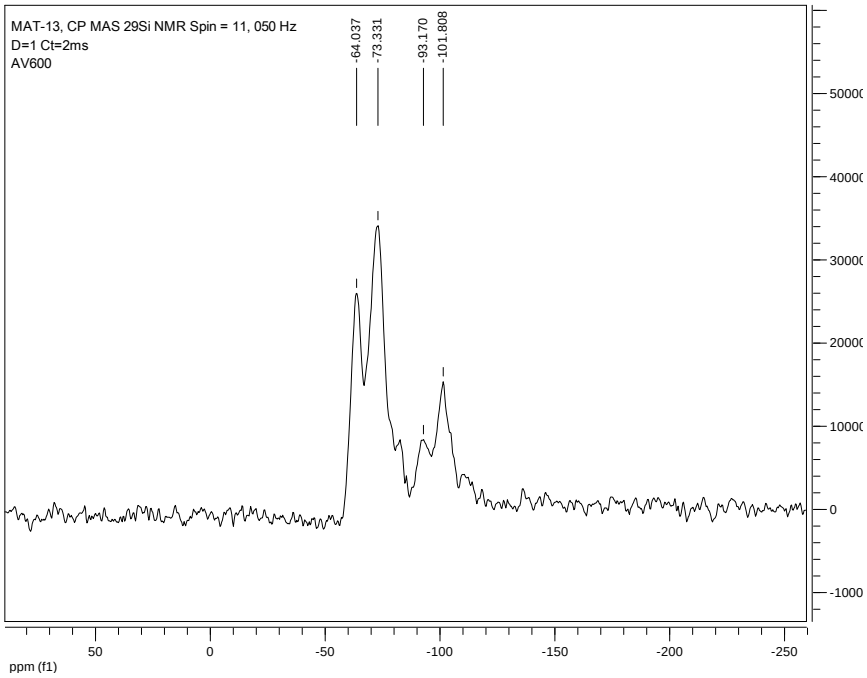
BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
19.4	818	0.454

N_2 adsorption of MAT13 and summary of critical parameters

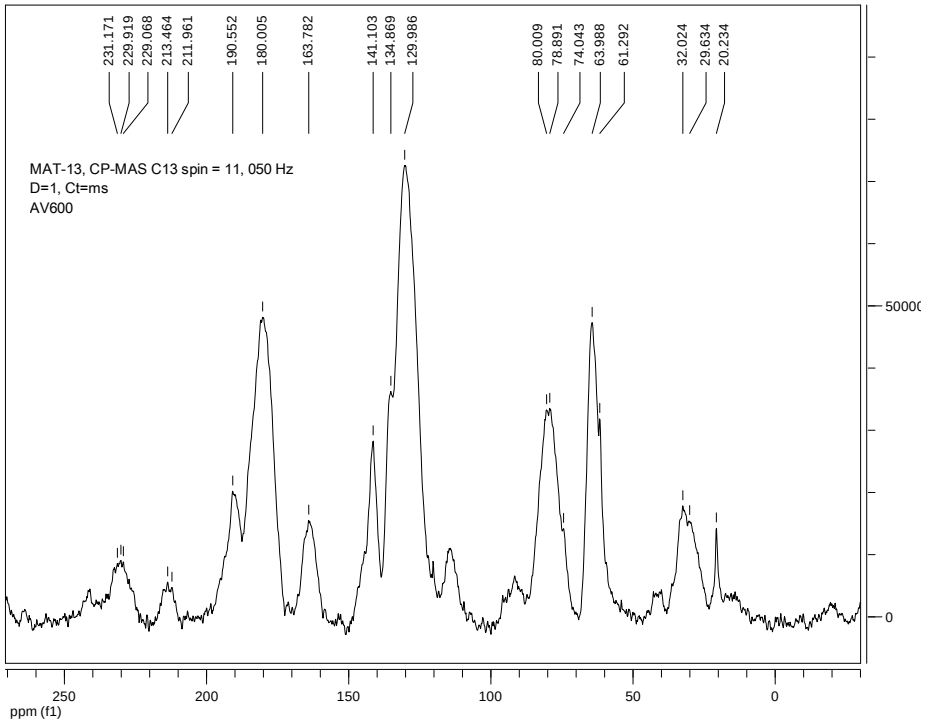


BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
17.6	376	0.191

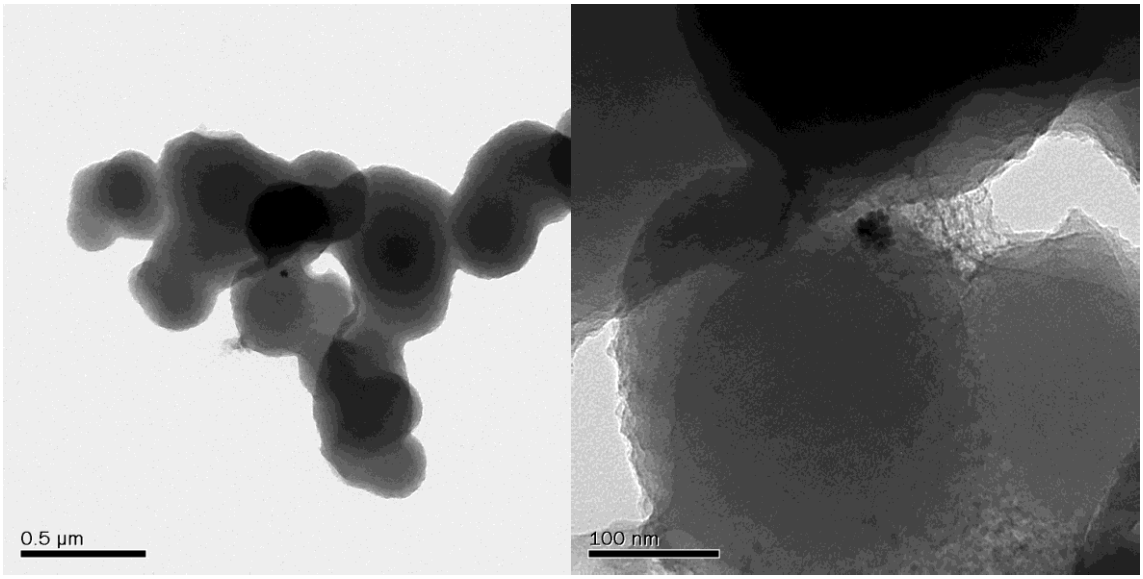
CP MAS ^{29}Si of MAT13

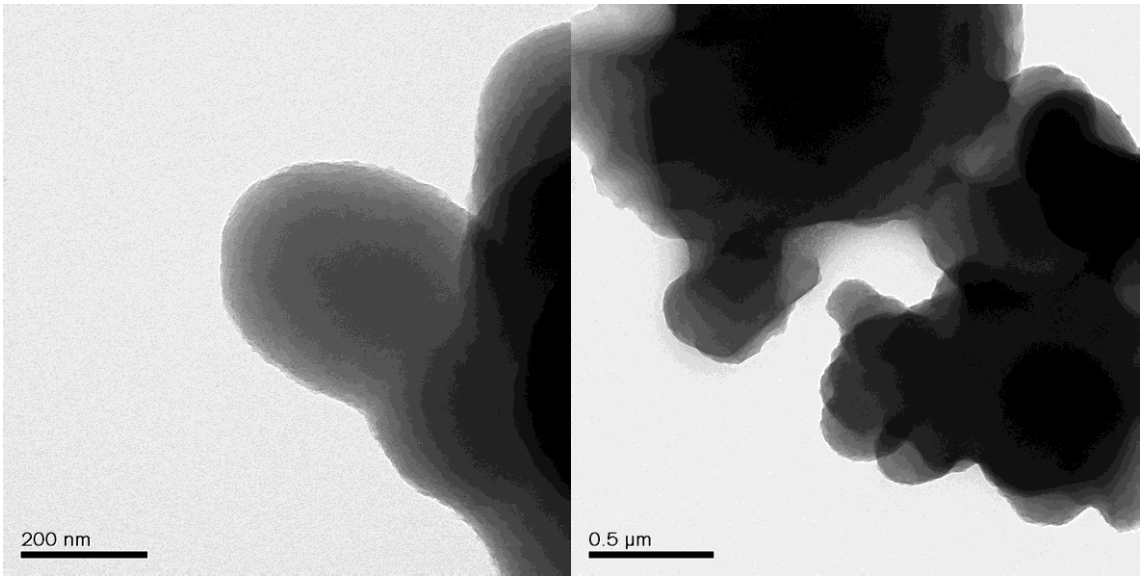


CP MAS ^{13}C NMR MAT13

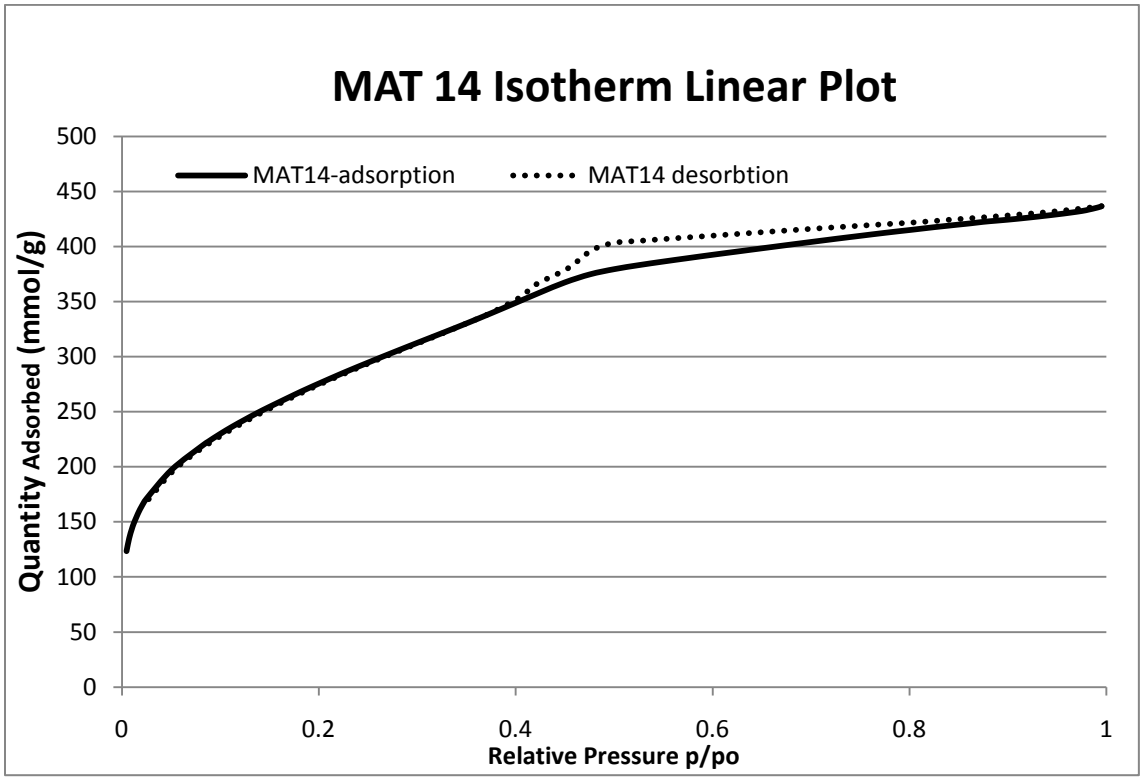


TEM Images of MAT 13



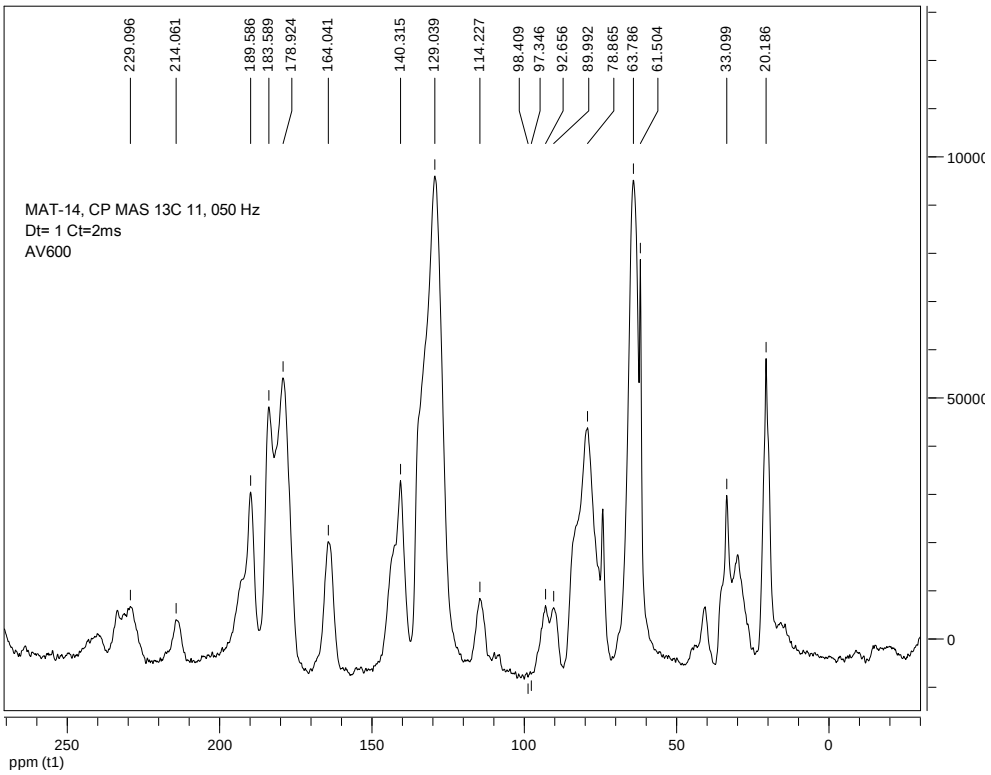


N_2 adsorption of MAT14 and summary of critical parameters

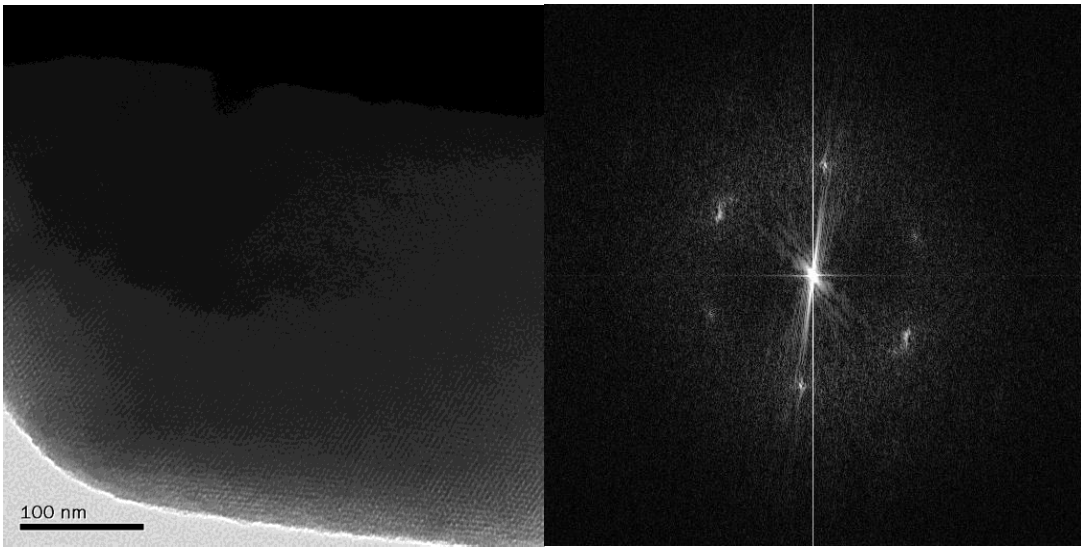


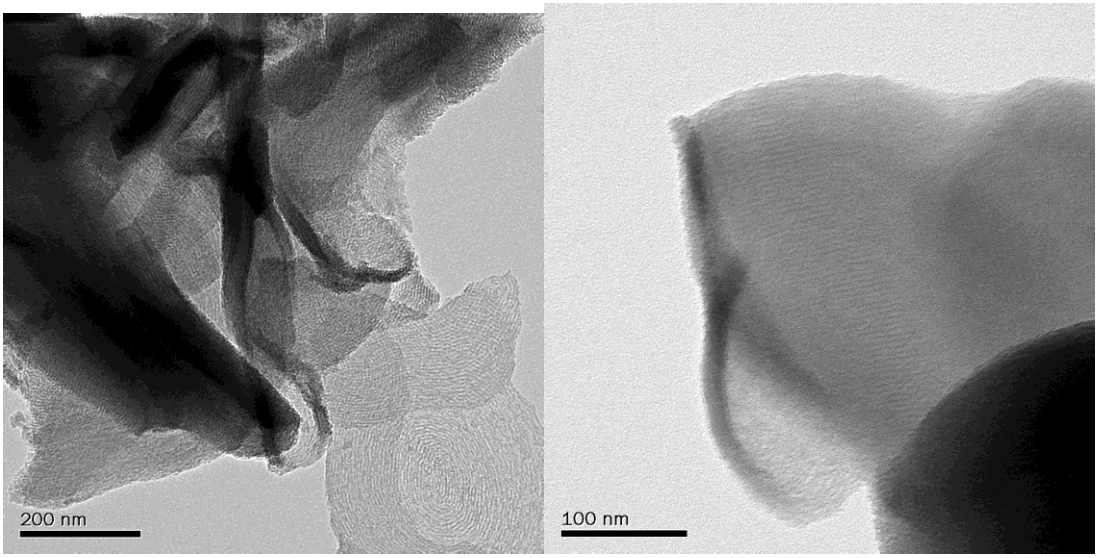
BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
22.6	1015	0.570

CP MAS ^{13}C NMR MAT 14

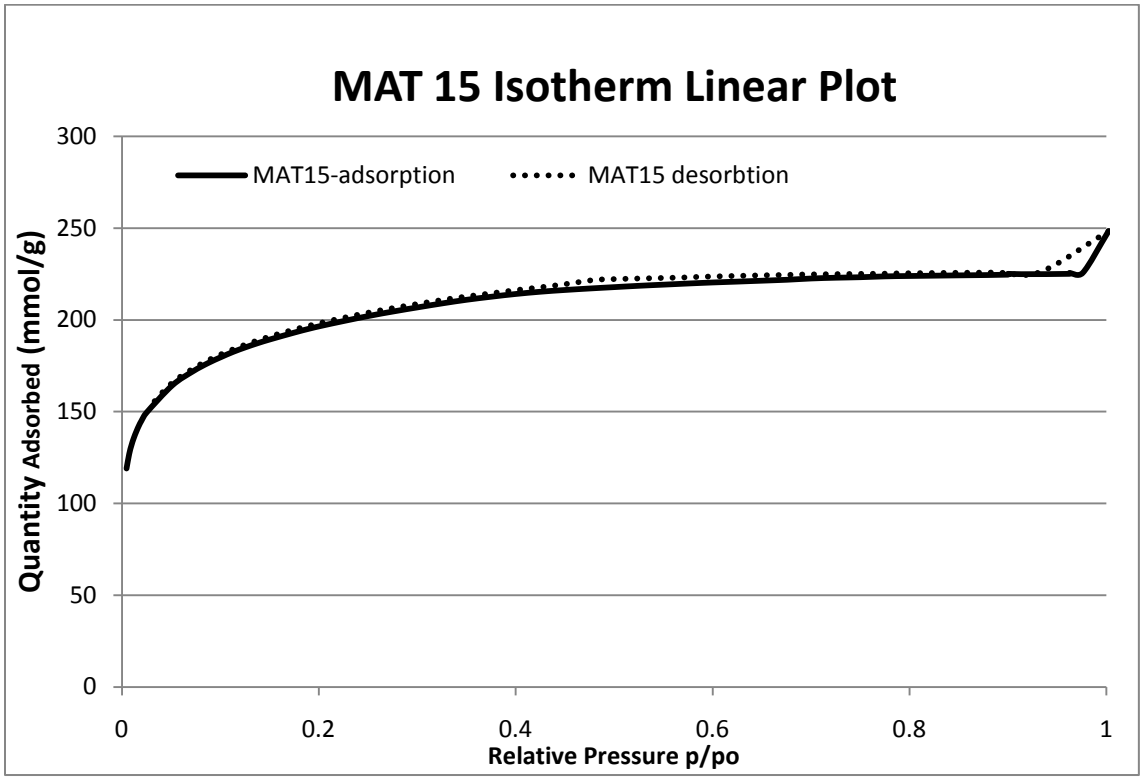


TEM images of MAT 14





N_2 adsorption of MAT15 and summary of critical parameters



BJH Pore Diameter Å	Surface Area m2/g	Pore Volume cm^3/g
22.6	679	0.363