Germyl Linker Cleavage with Carbon-Based Electrophiles

A thesis submitted towards the
fulfilment of the degree of PhD

By

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February 2004

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Abstract

This thesis describes the successful identification of a novel cross-coupling protocol for alkylaryldichlorogermanes, as part of an investigation towards the development of organogermanium linkers for solid phase synthesis. The application of Friedel-Crafts acylation towards the *ipso* degermylation of aromatic molecules with concomitant introduction of acyl functionality is also described.

By way of introduction, an in depth review of the literature surrounding Group 14 organometallic cross-couplings is presented, concentrating on the recent developments in the area of organosilicon and organogermanium cross-coupling chemistry. This is followed by a review of the literature precedent for *ipso* acyldesilylation and acyldestannylation of aromatic molecules.

Results are then presented that detail the work carried out towards successful arylgermane cross-coupling. Following extensive study and attempted optimisation of trialkylarylgermane cross-couplings, it was discovered that the incorporation of heteroatoms onto the germanium centre was necessary to obtain synthetically acceptable cross-coupling yields.

Further results are also presented in relation to acyldegermylation studies that illustrate the reactivity of arylgermanes towards acyl electrophiles, and the effect on acyldegermylation of varying the electronic nature of the aryl group attached to germanium.

Acknowledgements

I would like to extend my heartfelt gratitude to my supervisor Dr Alan Spivey for his essential guidance, patience and eternal optimism. The support and help from my industrial supervisors Dr Jan Scicinski and Dr Nigel Parr has also been invaluable during my studies. The help that my supervisors have provided over the last three years has been crucial in bringing this project to a successful conclusion.

I would also like to thank all the students in the Spivey research group over the last four years. I would especially like to thank Nonny Jones and David Turner, who have also worked on organogermanium chemistry, for their contributions and helpful discussions.

The support of the technical staff in the University of Sheffield Chemistry Department has also been invaluable. In particular I am grateful to Simon Thorpe and Jane Stanbra for mass spectrometry analyses, Alan Jones for elemental analyses, Dr Brian Taylor and Sue Bradshaw for NMR experiments, Dan Jackson and the late John Murray for their glassblowing expertise, Pete Farran and Nick Smith for technical assistance in the chemical stores, and Keith Owen for technical assistance in the laboratory.

Finally I would like to thank my parents, Kevin and Sue, and my wife Lucy for their indispensable emotional and financial support during my time in Sheffield, and also all my friends and lab colleagues for their assistance and encouragement.

Contents

Abbreviations

AcCl	Acetyl chloride
APC dimer	Allylpalladium(II) chloride dimer $(C_3H_5PdCl)_2$
aq	Aqueous
b	Broad
Binap	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BnTMAF	Benzyltrimethylammonium fluoride
Bu	Butyl
ca.	*Circa* (Latin "about")
Celite®	A high grade diatomaceous earth used as a filter aid.
CI	Chemical ionisation
cod	Cyclooctadiene
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
CSI	Chlorosulfonyl isocyanate
d	Doublet
DABCO	Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DIBAL	Diisobutylaluminium hydride
DMA	*N,N*-Dimethylacetamide
DMAP	*N,N*-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
Dppe	1,2-Bis(diphenylphosphino)ethane
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
Dppp	1,3-Bis(diphenylphosphino)propane
ee	Enantiomeric excess
e.g.	*Exempli gratia* (Latin "for example")
EI	Electron impact
ESI	Electrospray ionisation
Et	Ethyl

Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FIA	Flow injection analysis
GC	Gas chromatography
GC/MS	Gas chromatography-mass spectrometry
c.HCl	Concentrated aqueous HCl, 37% w/v, 10M
Hex	Hexyl
HRMS	High resolution mass spectrometry
i.e.	*Id est* (Latin "that is")
IMes·HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride
IPr·HCl	1,3-Bis(2,6-diispropylphenyl)imidazolium chloride
LC/MS	Liquid chromatography-mass spectrometry
Me	Methyl
MeCN	Acetonitrile
$MeNO_2$	Nitromethane
mp	Melting point
MS	Mass spectrometry
MSA	Methanesulfonic acid
n- or *normal*	normal
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
OAc	Acetate
OTf	Trifluoromethanesulfonyl
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Ph	Phenyl
$P(Mes)_3$	Tris-(2,4,6-trimethylphenyl)phosphine
PPh_3	Triphenylphosphine

ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
i-Pr	*iso*-Propyl
psi	Pounds per square inch (pressure)
q	Quartet
RCM	Ring closing metathesis
R_f	Retention factor
R_t	Retention time
rt	Room temperature
s	Singlet
s- or *sec*	Secondary
SPE	Solid phase extraction
t	Triplet
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBAOH	Tetra-*n*-butylammonium hydroxide
TBAT	Tetra-*n*-butylammonium triphenyldifluorosilicate
t- or *tert*	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMAF	Tetramethylammonium fluoride
TMDS	Tetramethyldisiloxane
TMG-Br	Trimethylgermanium bromide
TMS-Cl	Trimethylchlorosilane
Tol	*para*-Tolyl
Ts	*para*-Toluenesulfonyl

1 Introduction to cross-coupling

1.1 Group fourteen organometallic cross-coupling reactions

Control of carbon-carbon bond formation is invariably a key issue in the synthesis of even moderately complex organic molecules. One of the most important methods of carbon-carbon bond formation is by cross-coupling. The reaction of an organometallic complex with an organic (pseudo)halide in the presence of a palladium catalyst provides an elegant and efficient route for carbon-carbon bond formation, especially between unsaturated centres. The most common cross-coupling methods in use today are the Suzuki reaction of organoboron compounds,[1] the Stille reaction of organostannanes,[2-4] and to a lesser extent the Negishi reaction of organozincates.[5,6] Notwithstanding the wide utility of these methods, all have significant drawbacks from a synthetic standpoint: organoboronic acids and esters can be difficult to synthesise and purify and are unstable to many reaction conditions,[1] organostannanes and their halostannane by-products are highly toxic and atom inefficient,[7] whilst organozincates are highly reactive and difficult to prepare.

In the case of the Stille reaction with organotin reagents there are many variations, and only the mechanistic details of the transformation will be considered in depth here. Detailed discussions on the scope of the Stille reaction and the versatility of organotin reagents in synthesis can be found in the reviews written by Stille, Mitchell and Davies.[3,4,8,9]

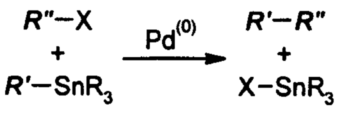
It was not until Hiyama's pioneering work with fluorosilanes in the late 1980's that it was recognised that the inherent unreactivity of organosilanes and germanes towards cross-coupling, resulting from the absence of a significant dipole across C-Si and C-Ge bonds as compared to C-Sn bonds, could be overcome.[10] Furthermore, organosilanes and germanes have the advantage that they are generally non-toxic.[11,12] Fluorosilanes, however, are not particularly attractive coupling partners from a synthetic standpoint as they are inconvenient to prepare and unstable towards chromatography. Subsequent efforts by various groups have therefore been directed towards the development of readily accessible organosilane and organogermane derivatives that retain the favourable handling and cross-coupling characteristics of organostannanes but without the associated toxicity. Significant progress towards this end has now been achieved and will be described in some detail.

Organogermane cross-coupling reactions have been much less widely explored than their organosilane counterparts, probably in part due to the higher cost of germanium relative to silicon. Germanium-carbon bonds are intermediate between silicon-carbon and tin-carbon bonds in terms of their reactivity towards electrophiles.[13] Considering the ability of organotin and activated organosilicon compounds to cross-couple it seems likely that an appropriately activated organogermanium compound should also undergo cross-coupling reactions. There are three reported examples of heavily activated organogermanes undergoing a cross-coupling reaction and these will also be discussed.

1.2 Organotin cross-coupling reactions

The palladium(0) catalysed cross-coupling of an organostannane with an organohalide is known as the Stille reaction, and is a widely used method of carbon-carbon bond formation in unsaturated systems. The reaction has been comprehensively studied, and has found widespread synthetic application.

The scope of organotin cross-coupling chemistry will only be briefly considered here, with discussion concentrating on cross-coupling reactions involving hypervalent tin species, and the mechanism of coupling. Both of these subjects have a direct bearing on the cross-coupling reactions of other hypervalent group 14 organometallic compounds, which are extensively discussed later in this chapter.



$$\begin{matrix} R''\text{—}X \\ + \\ R'\text{—}SnR_3 \end{matrix} \xrightarrow{Pd^{(0)}} \begin{matrix} R'\text{—}R'' \\ + \\ X\text{—}SnR_3 \end{matrix}$$

Figure 1.1 General form of a Stille coupling between organotin and organohalide residues[3,4]

The cross-coupling of an organotin species was first observed by Migita,[14,15] but was further developed and popularised by Stille.[16,17] The use of phosphine co-catalysts to improve yields and extend the scope of the reaction has been investigated by others, most notably Farina.[2,18]

The reaction is synthetically useful because it provides an attractive and simple means of constructing many commonly observed chemical moieties, most especially biaryl units and conjugated alkene systems that can be difficult to construct *via* other methods. The organostannane reagents themselves are stable to air and moisture, and withstand common separation techniques, such as distillation or silica chromatography. The reagents are also easy to synthesise and are often commercially available. They possess low nucleophilicity compared to Grignard organomagnesium reagents, organolithium reagents or Negishi organozincate reagents, which in turn means that they are compatible with a much greater range of functional groups within either of the coupling partners.[4] The main drawback with organotin reagents is their acute toxicity, especially the triorganotin halide by-products.[8,9,19]

The organic group transferred from tin can be alkynyl, alkenyl, aryl, benzyl, or allyl,[3,4] although transfer of alkyl groups has also been reported.[3,4,20] The order of reactivity of these groups is accepted to be alkynyl > alkenyl > aryl > allyl > benzyl >> alkyl. Only one group will routinely be transferred from tin, as the triorganotin halide by-product reacts at least a hundred times slower than the parent tetraorganotin.[4] The other three ligands at the tin centre are usually either methyl or butyl, both of which are resistant to transfer in the presence of more reactive organic groups, and behave as non-transferable dummy ligands. Butyl groups are usually preferred as they lessen both the volatility and the toxicity of the reagent. This design of the organotin reagent leads to the selective transfer of only one group from tin.

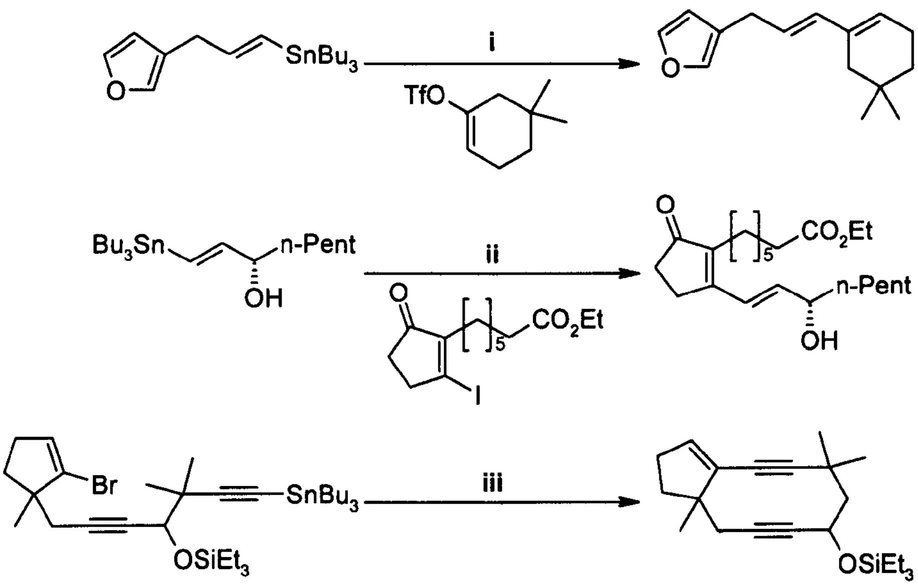


Figure 1.2 Examples of Stille couplings[3]

Reagents and conditions: i) Pd(PPh$_3$)$_4$, LiCl, THF, 66°C, 24h, 75%;[21] ii) [(PhCH$_2$)Pd(PPh$_3$)$_2$(Cl)], THF, 60°C, 36h, 73%;[22] iii) Pd(PPh$_3$)$_4$, THF, 50°C, 86h, 72%.[23]

The (pseudo)halides used in Stille couplings are usually β-unsaturated bromides, iodides, or triflates.[18] Organochlorides are traditionally very unreactive in Stille cross-coupling reactions due to a reluctance to undergo oxidative addition with palladium, although recent developments of the phosphine co-catalyst have overcome this limitation.[24] The organic group of the halide generally must not possess sp^3 hydrogens β to the halogen, as β hydride elimination to generate an alkene from the σ-palladium(II) intermediate is a much faster process than the desired transmetallation step. As a result the organohalides are generally alkenyl, allyl, aryl or benzyl compounds.[4] However, very recent advances with phosphine co-catalysts, related to the activation of aryl chlorides, have been made to facilitate the coupling of organostannanes and alkyl halides possessing β- hydrogens.[25,26]

1.2.1 Organotin cross-coupling mechanism

The traditionally accepted mechanism of cross-coupling follows a four stage catalytic cycle:

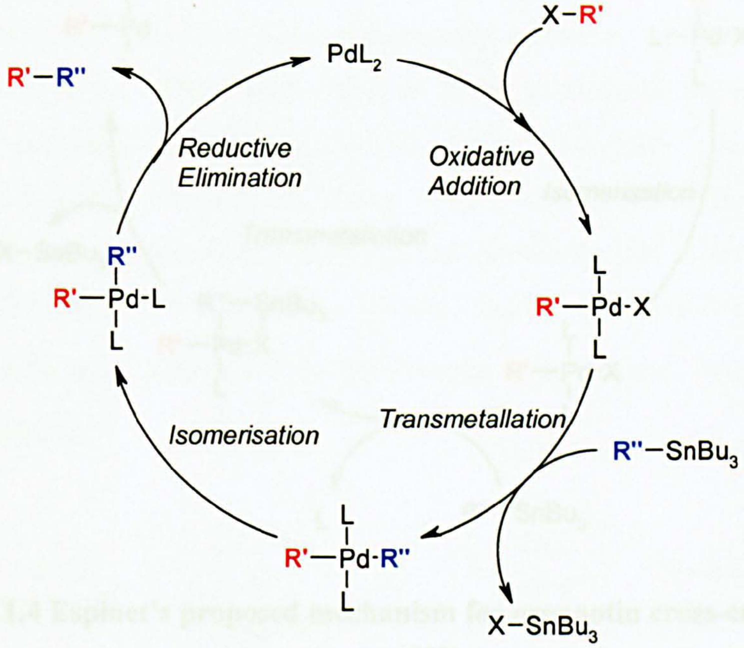


Figure 1.3 Traditional mechanism of organotin cross-coupling reactions[3,4]

However, this mechanism has been convincingly criticised by Espinet, who has carried out several detailed kinetic and mechanistic studies and proposed several refinements.[27,28] Espinet's reasoning is quite detailed and will not be reproduced here, although the chemistry involved in each step will be outlined. For the purposes of this report Espinet's mechanism will be used as the model for Stille reactions, and other group 14 organometallic cross-couplings.

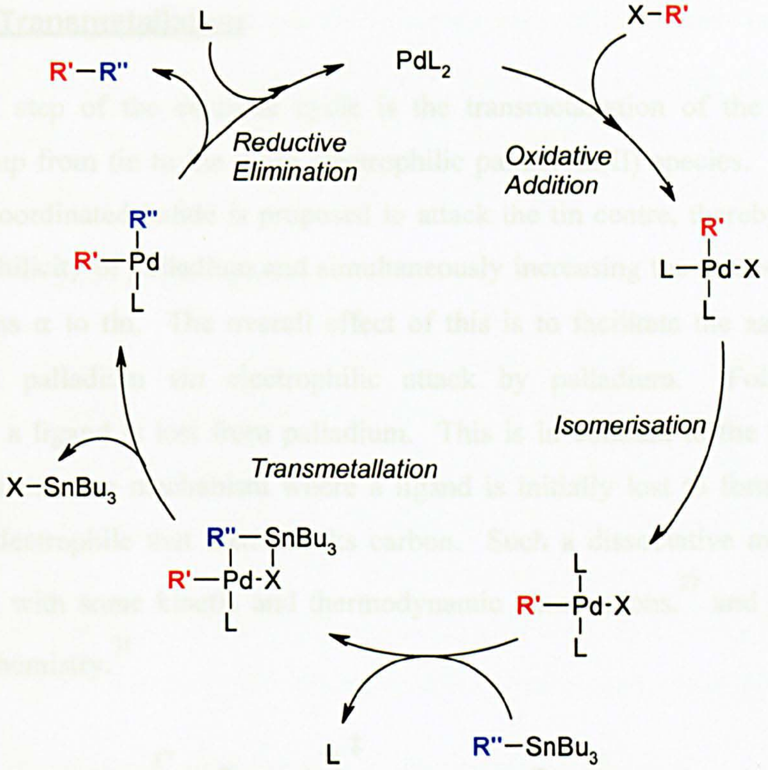


Figure 1.4 Espinet's proposed mechanism for organotin cross-coupling reactions.[27,28]

1.2.1.1 Oxidative addition

The first step of the mechanism is oxidative addition of the organohalide to the palladium(0) catalyst. This is believed to occur *via* the nucleophilic displacement of halide by a coordinatively unsaturated palladium(0) 14 electron species, and gives rise initially to a square-planar *cis*-[PdR'XL_2] complex. This *cis*-Pd complex then isomerises to a *trans*-[PdR'XL_2] compound, which can autocatalyse the isomerisation.[29]

The order of reactivity of the organohalides to oxidative addition is I > Br ≈ OTf >> Cl.[30] The rate of insertion is enhanced by the presence of strong σ-donor ligands such as trialkylphosphines, which increase electron density on palladium, thereby increasing its nucleophilicity.

1.2.1.2 Transmetallation

The second step of the catalytic cycle is the transmetallation of the unsaturated organic group from tin to the more electrophilic palladium(II) species. Initially the palladium coordinated halide is proposed to attack the tin centre, thereby increasing the electrophilicity of palladium and simultaneously increasing the nucleophilicity of carbon atoms α to tin. The overall effect of this is to facilitate the association of carbon and palladium *via* electrophilic attack by palladium. Following this association, a ligand is lost from palladium. This is in contrast to the traditionally accepted dissociative mechanism where a ligand is initially lost to form a trivalent palladium electrophile that then attacks carbon. Such a dissociative mechanism is inconsistent with some kinetic and thermodynamic observations,[27] and with known palladium chemistry.[31]

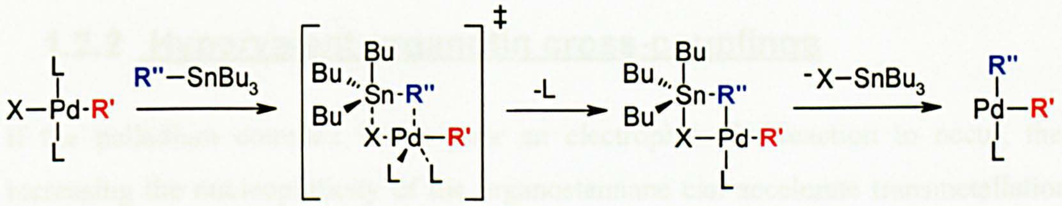


Figure 1.5 Associative mechanism of transmetallation[27]

The proposed associative mechanism for transmetallation generates a T-shaped *cis*-[PdR'R"L] species which is able to immediately participate in a reductive elimination process. The implication of a hypervalent tin species in the transition state and transmetallation intermediate clearly suggests that coordinate unsaturation of the metal centre is a necessary requirement of the organometallic coupling partner.

Due to the electrophilic nature of the palladium(II) centre in this step, transmetallation is favoured by factors that reduce its electron density. This includes phosphine ligands that are good electron acceptors and preferably also poor electron donors, although in reality the choice of ligand is a compromise between the reactivity of the catalyst towards oxidative addition and transmetallation. Another factor that influences electron density on palladium is the nature of the coordinated halide. The order of reactivity for the transmetallation step in terms of the halides present is Cl > Br > I.[32] It is for this reason that triflates are commonly used, as they readily undergo oxidative addition to palladium(0), yet in the presence of chloride can be readily exchanged, to generate a more reactive organopalladium(II) chloride species.

1.2.1.3 Reductive elimination

Transmetallation gives a T-shaped palladium(II) complex with the organic ligands *cis* to each other. The final step of the mechanism is the reductive elimination of the two organic ligands on palladium(II), to form the coupled product and regenerate the coordinatively unsaturated palladium(0) catalyst. Bond formation in a reductive elimination process is the result of orbital overlap between the two eliminating ligands. Consequently, reductive elimination is promoted by ligands that possess a large steric bulk, which force the organic ligands spatially closer together.

1.2.2 Hypervalent organotin cross-couplings

If the palladium complex is too poor an electrophile for reaction to occur, then increasing the nucleophilicity of the organostannane can accelerate transmetallation. Intramolecular chelation of tin by amines to form a hypervalent tin centre has been demonstrated to increase reactivity of organostannanes towards palladium electrophiles. Vedejs has reported a carbastannatrane compound, where the tin centre is intramolecularly chelated by nitrogen, and is then sufficiently reactive to transfer a methyl group.[20]

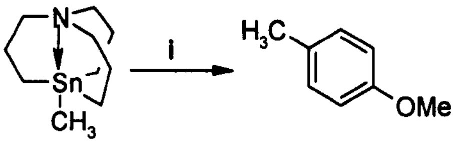


Figure 1.6 Methyl transfer from Vedejs' carbastannatrane

Reagents and conditions: i) 4-bromoanisole, PdCl$_2$(dppf), toluene, 75°C, 2h, 94%.

In a complementary study Brown has shown that a dimethylbenzylaminotin complex reacts a hundred times faster than the analogous compound with a methyl group in place of the dimethylamino moiety.[33]

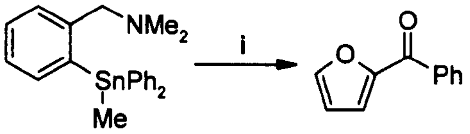


Figure 1.7 Increase in the rate of phenyl transfer due to intramolecular chelation

Reagents and conditions: i) 2-furanoyl chloride, [*trans* $Pd(PhCO)(Cl)(PPh_3)_2$], THF, 65°C.

The formation of a hypervalent tin compound is not only limited to compounds where a pendant ligand is able to intramolecularly coordinate to the tin centre. In order for oxidative addition to occur with aryl chlorides Fu developed a $Pd_2dba_3/P(t\text{-}Bu_3)_2$ catalyst system. However the presence of two exceptionally strongly electron-donating phosphines then completely inhibits the transmetallation step. In order to overcome this, Fu also added an intermolecular fluoride source to form a hypervalent tin species that is more reactive towards the electron rich palladium(II) species.[34]

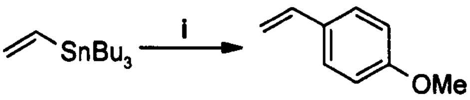
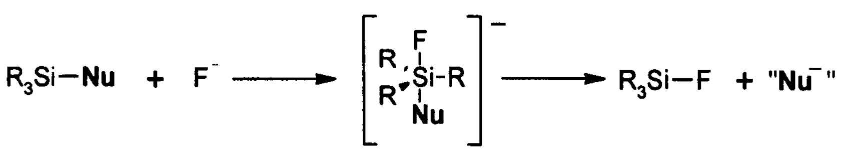


Figure 1.8 Activation of organotin complexes by intermolecular fluoride

Reagents and conditions: i) 4-chloroanisole, $Pd_2(dba)_3$, $P(t\text{-}Bu)_3$, CsF, 1,4-dioxane, 100°C, 48h, 82%.

1.3 Organosilicon cross-coupling reactions

Organosilanes are inherently less polar, and therefore less reactive, than organostannanes. Hiyama overcame this problem through the coordination of a fluoride nucleophile to the silicon centre, thereby increasing the reactivity of axial ligands α to the metal centre.[35-40]

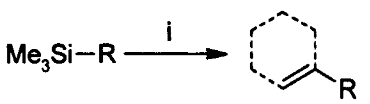


Nu = H, $SiMe_3$, $CH_2CH{=}CF_2$, $CF{=}CF_2$, $CHCl_2$, CCl_3, C_6F_5

Figure 1.9: Increasing reactivity of ligands at silicon *via* coordination of fluoride

1.3.1 Cross-coupling of alkyl and halo silanes

Heck-type couplings of organosilanes had been previously described by Kumada,[41] Hallberg[42] and Matsuda.[43] In 1988 Hiyama extended his use of nucleophiles to activate organosilanes and described the first coupling of a organosilanes with aryl halides mediated by intermolecular fluoride and proceeding *via* a Stille-type mechanism.[44]



Reagents and conditions: i) organic halide, APC dimer, TASF, Solvent, 50°C.

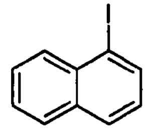
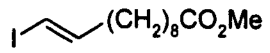
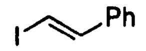
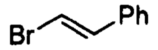
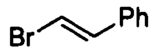
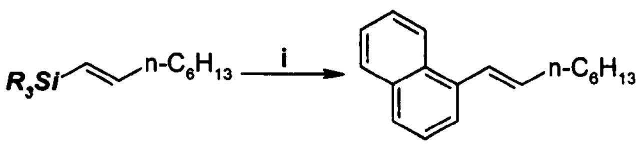
R	Organic Halide	Conditions	Yield
Vinyl		HMPA	98%
Vinyl		HMPA/P(OEt)$_3$	88%
E-Styryl		HMPA/P(OEt)$_3$	32%
Phenylethynyl		THF	83%
Allyl		THF	28%

Figure 1.10: Cross-coupling of trimethylsilyl compounds with TASF activator

Despite the success of vinyl- and alkynyl trimethylsilanes as coupling partners, substituted alkenyl- and allyl trimethylsilanes did not react in satisfactory yield under these conditions. This led Hiyama to introduce electron-withdrawing substituents onto silicon; this was designed to activate the system by increasing the polarity of the silicon-carbon bond and facilitating coordination of the fluoride to the silicon centre.[45]



Reagents and conditions: i) APC dimer, TASF, THF, 50°C.

***SiR*$_3$**	**Reaction time**	**Yield**
$SiMe_3$	24h	0%
$SiMe_2F$	10h	81%
$SiMeF_2$	48h	74%
SiF_3	24h	0%

Figure 1.11: Cross-coupling of fluorosilanes

Mono- and difluorosilanes were found to be optimal substrates in these reactions whereas trifluorosilanes were wholly unreactive. Hiyama suggested that this was most likely due to the formation of co-ordinately saturated hexavalent pentafluorosilicate species. A similar pattern emerged for *aryl*silane cross-coupling to give biaryls,[46] a reaction that could also be performed in the presence of carbon monoxide to give diarylketones.[47] Trifluorosilane derivatives were however required for cross-coupling of α-substituted benzyl substrates with aryl triflates. At temperatures below 70°C these transformations were shown to proceed with complete retention of configuration at the α-stereocentre.[48]

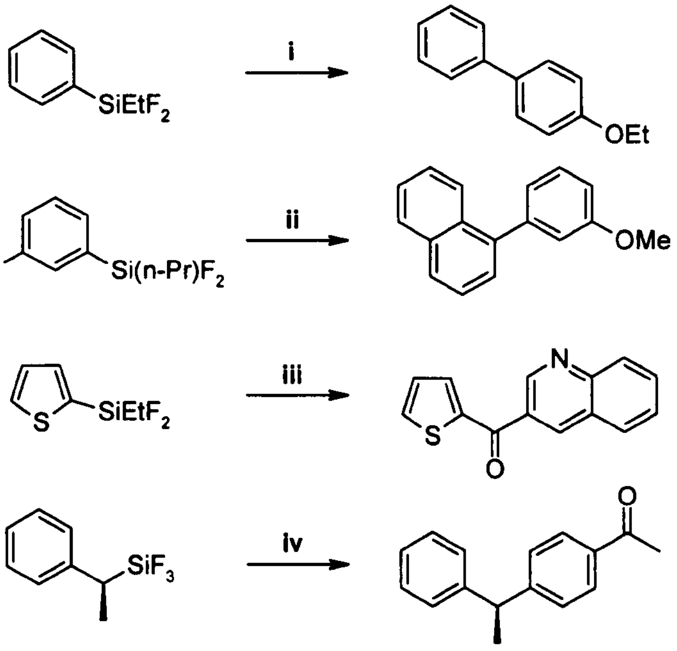


Figure 1.12: Cross-coupling of organosilanes

Reagents and conditions: i) 4-Iodoethoxybenzene, APC dimer, KF, DMF, 70°C, 81%; ii) 1-iodonaphthalene, APC dimer, KF, DMF, 100°C, 94%; iii) 3-iodoquinoline, APC dimer, CO, KF, DMF, 100°C, 78%; iv) trifluoromethyl *p*-acetophenyl sulfonate, $Pd(PPh_3)_4$, TBAF, THF, 50°C, 51%.

Cross-coupling of *alkyl* groups using fluorosilanes was also found to be possible. Hiyama noted that in the absence of organosilanes, TASF ($[Me_3SiF_2]^-$ $[(Et_2N)_3S]^+$) itself reacts as a coupling partner and methylates various aryl halides and alkenyl iodides.[49]

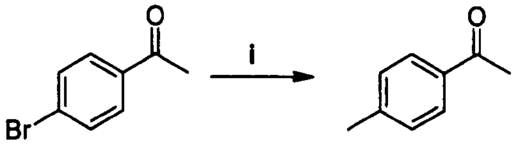
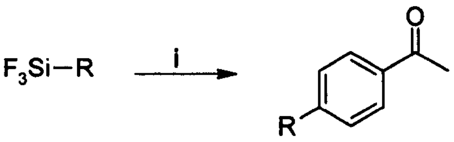


Figure 1.13: Methylation of 4-bromoacetophenone with TASF

Reagents and conditions: i) TASF, APC dimer, THF, 50°C, 82%

Subsequently, alkyl trifluorosilanes in combination with tetrabutylammonium fluoride (TBAF) and $Pd(PPh_3)_4$ were shown to be effective for coupling of various alkyl groups to aryl bromides and iodides in moderate to good yields.[50,51]



Reagents and conditions: i) 4-bromoacetophenone, $Pd(PPh_3)_4$, TBAF, THF, 100°C.

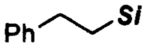
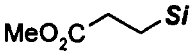
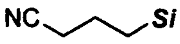
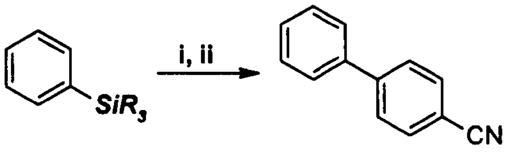
R	Yield
$n\text{-}C_6H_{13}\text{—}Si$	65%
 Ph *Si*	71%
 MeO_2C *Si*	72%
 NC *Si*	54%

Figure 1.14: Cross-coupling of alkylsilanes

Hiyama also demonstrated the ability of *chloro*silanes to undergo cross-coupling reactions in the presence of fluoride.[52] Although fluoro and chlorosilanes are both unstable to atmospheric conditions and chromatography, the ability to use chlorosilanes is advantageous as they are the precursors for the synthesis of fluorosilanes. Using chlorosilanes themselves avoids the need for an extra synthetic step using harmful and harsh fluorinating agents.



Reagents and conditions: i) KF, DMF, rt, 3h; ii) 4-bromobenzonitrile, Pd(OAc)$_2$, PPh$_3$, 120°C, 20h.

SiR$_3$	Yield
SiMe$_2$Cl	37%
SiMeCl$_2$	51%
SiEtCl$_2$	70%
SiCl$_3$	0%

Figure 1.15: Chlorosilane cross-coupling

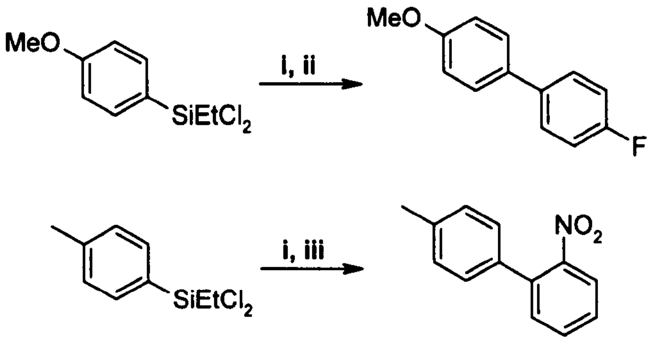
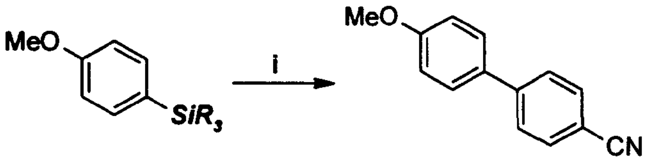


Figure 1.16: Chlorosilane cross-coupling examples

Reagents and conditions: i) KF, DMF, rt, 3h; ii) 4-bromofluorobenzene, Pd(OAc)$_2$, PPh$_3$, 120°C, 20h, 91%; iii) 2-bromonitrobenzene, Pd(OAc)$_2$, PPh$_3$, 120°C, 20h, 92%.

As with the fluoro analogues, dichloroalkylsilanes were the optimal coupling partners, and the trichloro analogue remained wholly inert. In the presence of Pd(0) and triisopropylphosphine, chlorosilanes activated by fluoride are also able to react with aryl chlorides.[53] The unreactivity seen for trifluorosilanes was not observed for the analogous trichlorosilanes.



Reagents and conditions: i) 4-chlorobenzonitrile, $(i\text{-}Pr_3P)_2PdCl_2$, KF, DMF, 150°C, 20h.

SiR$_3$	Yield
$SiMe_2Cl$	93%
$SiEtCl_2$	95%
$SiCl_3$	73%

Figure 1.17: Reactivity of chlorosilane cross-couplings with aryl chlorides

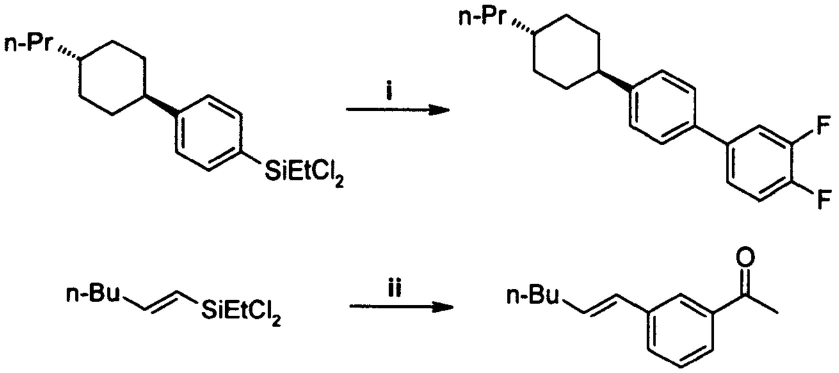
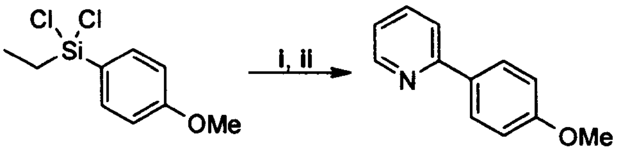


Figure 1.18: Examples of chlorosilane cross-couplings with aryl chlorides

Reagents and conditions: i) 3,4-difluorochlorobenzene, $(i\text{-}Pr_3P)_2PdCl_2$, KF, DMF, 150°C, 20h, 64%; ii) 3-chloroacetophenone, $(i\text{-}Pr_3P)_2PdCl_2$, KF, DMF, 150°C, 20h, 83%.

Hydroxide was also found to be a superior activator to fluoride for chlorosilane cross-couplings.[54]



Reagents and conditions: i) solvent, activator, rt 3h ii) 2-bromopyridine, $Pd(OAc)_2$, ligand.

Activator	Ligand	Solvent	Temperature	Time	Yield
KF	$P(o\text{-}Tol)_3$	DMF	120°C	18h	23%
NaOH	PPh_3	THF	60°C	39h	69%

Figure 1.19: Comparison of KF and NaOH activators for chlorosilane cross-couplings

Hiyama demonstrated the practicality of the chemistry that he had developed in the synthesis of an artificial HMG-CoA reductase inhibitor NK-104, which is indicated in the regulation of cholesterol biosynthesis. The key *E*-alkenyl chlorodimethylsilane cross-coupling substrate was prepared by hydrosilylation of a terminal alkyne.[55,56]

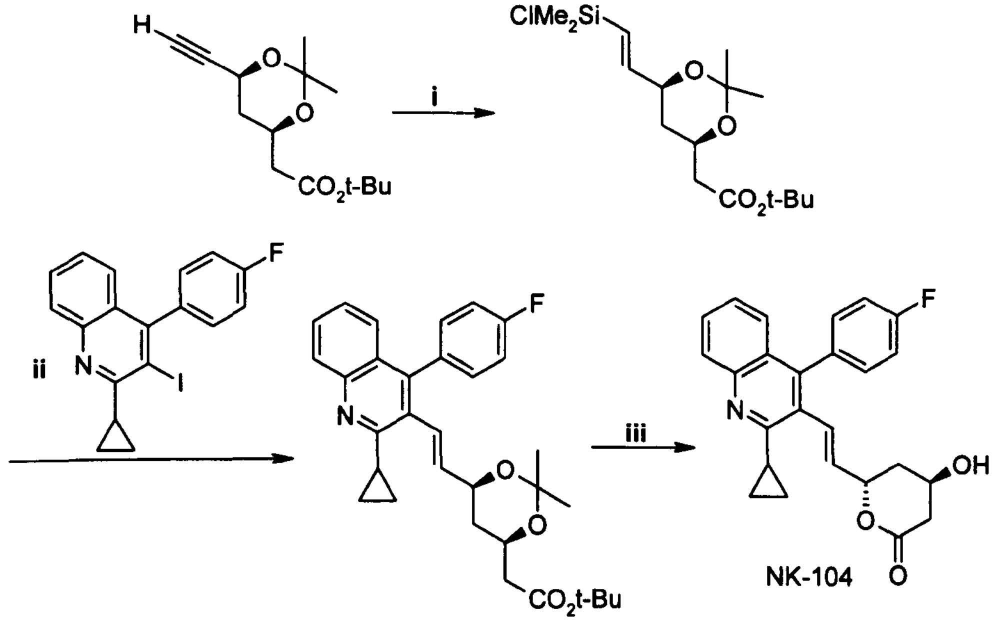
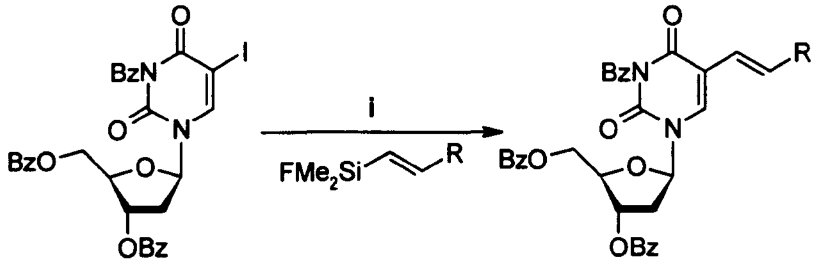


Figure 1.20: Synthesis of NK-104 *via* a silyl cross-coupling reaction

Reagents and conditions: i) Me_2ClSiH, $(t\text{-}Bu)_3P{\cdot}Pt(DVDS)$, rt, 1h; ii) APC dimer, aryl iodide, TBAF, THF, 60°C, 80% over 2 steps; iii) TFA, CH_2Cl_2, rt, 16h, 67%, 98% ee.

Hiyama also prepared 5'-substituted pyrimidine nucleosides with potential antitumour and antiviral activity using an *E*-alkenyl methyldifluorosilane cross-coupling protocol.[57]

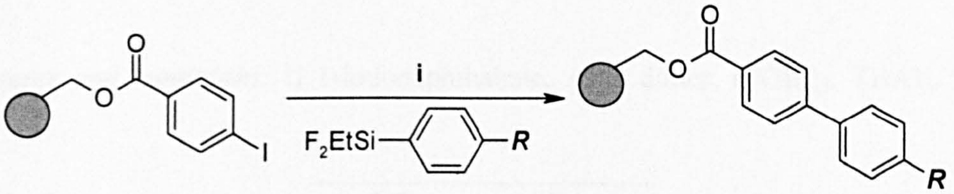


Reagents and conditions: i) APC dimer, TBAF, THF, 60°C

R	Yield
Phenyl	64%
n-C_6H_{13}	60%

Figure 1.21: Cross-coupling with iodopyrimidine nucleosides

More recently, aryl ethyldifluorosilanes have also been shown to react with Wang resin-bound aryl iodides.[58,59]



Reagents and conditions: i) $Pd(OAc)_2$, P(2-furyl)$_3$, KF, DMF, 120°C, 30h.

R	Conversion[(a)]
n-Butyl	100%
Methoxy	100%

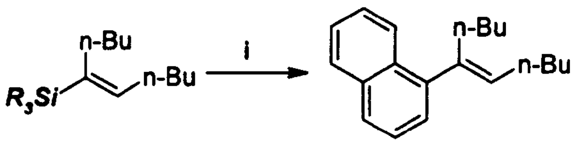
(a) Conversion estimated by ^1H NMR of cleaved coupled product

Figure 1.22: Cross-coupling with resin bound aryl iodides

Halosilanes are generally synthesised either by hydrosilylation of alkynes with chloroalkylsilyl hydrides to form alkenylsilanes (*e.g.* figure 1.20), or by the action of an aryl-metal on an appropriate silyl chloride electrophile.[52] Conversion of silyl chlorides to fluorides is generally achieved by the action of toxic and harmful fluorinating reagents such as SbF_3[60] or CuF_2.[61]

1.3.2 Cross-coupling of siloxanes

In 1989 Tamao disclosed that alkenylsiloxanes were also competent partners for cross-coupling with aryl iodides. Siloxanes offer advantages over halosilanes as they are easier to handle by virtue of being less Lewis acidic. Both monoalkoxy- and dialkoxysilanes coupled in high yield with 1-iodonaphthalene using allyl palladium chloride dimer as catalyst, triethylphosphite as ligand and TBAF as fluoride source. Trialkoxysilanes coupled in poorer yields, possibly due to a tendency to form unreactive hexavalent coordinatively saturated species under the coupling conditions.[62]



Reagents and conditions: i) 1-iodonaphthalene, APC dimer, P(OEt)$_3$, TBAF, THF, 50°C.

SiR$_3$	Yield
SiMe$_2$(OEt)	95%
SiMe(OEt)$_2$	96%
Si(OEt)$_3$	54%

Figure 1.23: Reactivity of alkenyl siloxanes

Tamao also reported the intramolecular hydrosilylation of a homopropargylic alcohol followed by cross-coupling to give trisubstituted homoallylic alcohols.[62]

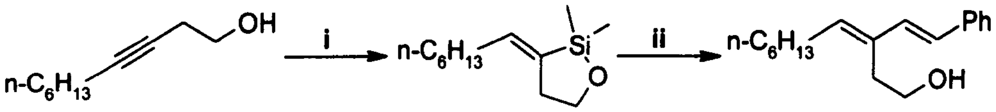


Figure 1.24: Hydrosilylation cross-coupling protocol

Reagents and conditions: i) (HMe$_2$Si)$_2$NH, H$_2$PtCl$_6$·6H$_2$O, CH$_2$Cl$_2$, rt; ii) *E*-2-bromostyrene, APC dimer, P(OEt)$_3$, TBAF, THF, 50°C; 42% over two steps.

This type of coupling was applied to the formal synthesis of the antileukaemic substance nitidine chloride.[63]

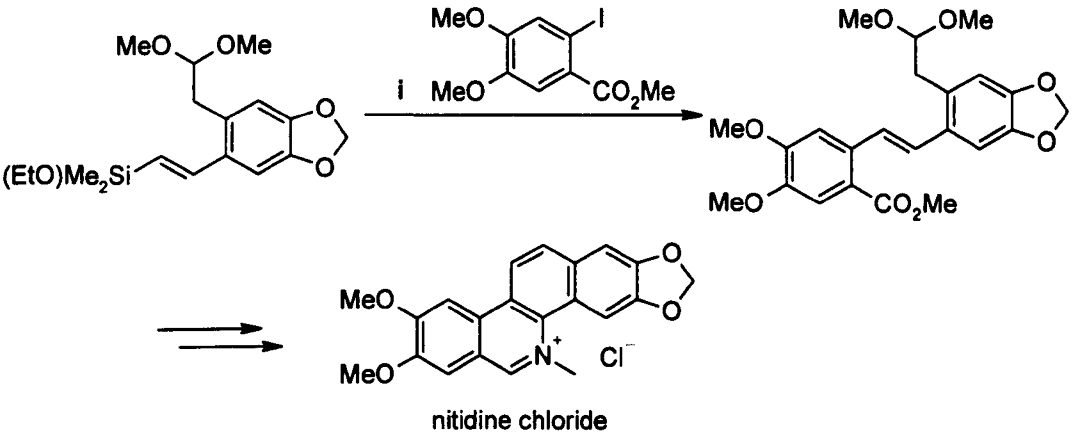


Figure 1.25: Synthesis of nitidine chloride *via* a siloxane cross-coupling protocol

Reagents and conditions: i) aryl iodide, APC dimer, $P(OEt)_3$, TBAF, THF, 60°C; 76%.

Shibata was the first to investigate *aryl* trimethoxysilanes as coupling partners with aryl bromides for the synthesis of substituted biaryls. Representative of a large number of biaryls prepared in this manner was 4-(*trans*-4-*n*-propylcyclohexyl)-3',4'-difluorobiphenyl which is used in active matrix liquid crystal displays.[64]

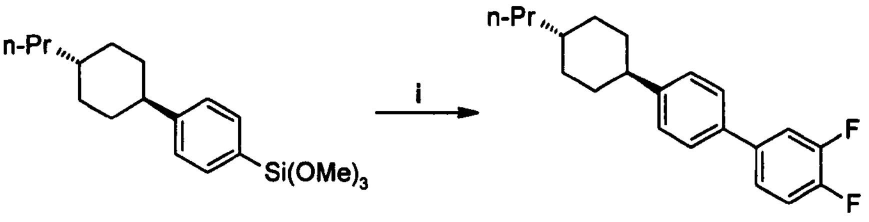
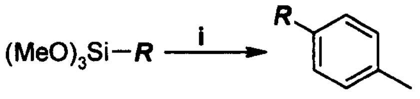


Figure 1.26: Aryl siloxane cross-coupling

Reagents and conditions: i) 3,4-difluorobromobenzene, $Pd(OAc)_2$, PPh_3, TBAF, toluene, 110°C, 90%.

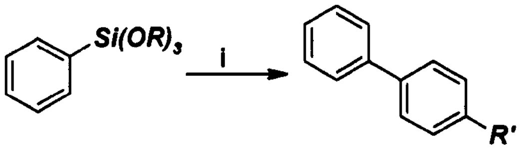
Subsequently, DeShong expanded the scope of this type of cross-coupling yet further to encompass efficient coupling with both electron deficient and electron rich aryl bromides and iodides.[65-67]



Reagents and conditions: i) 4-iodotoluene, Pd(dba)$_2$, TBAF, DMF, 85°C.

R	Yield
Vinyl	63%
Phenyl	90%
Allyl	60%

Figure 1.27: DeShong's cross-coupling of organotrimethoxysilanes

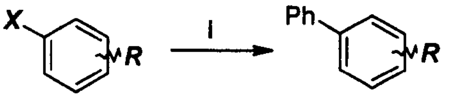


Reagents and conditions: i) aryl iodide, Pd(dba)$_2$, TBAF, DMF, 85°C.

Si(OR)$_3$	Aryl iodide	Yield
Si(OMe)$_3$	*p*-Acetyl	58%
Si(OMe)$_3$	*p*-Anisyl	54%
Si(OCH$_2$CF$_3$)$_3$	*p*-Tolyl	97%
Si(OCH$_2$CF$_3$)$_3$	*p*-Anisyl	77%

Figure 1.28: DeShong's cross-coupling of phenyl trialkoxysilanes with various aryl iodides

DeShong's initial cross-coupling conditions were only reactive when using aryl iodides, and he later reported an improved catalytic system, which could even couple aryl chlorides and aryl trisiloxanes when using Buchwald's 2-(dicyclohexylphosphino)biphenyl ligand.[68]

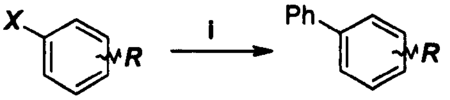


Reagents and conditions: i) Ph-Si(OMe)$_3$, Pd(OAc)$_2$, ligand, TBAF, DMF, 85°C.

R	Halide	Ligand	Yield
p-Acetophenyl	Br	PPh$_3$	86%
p-Tolyl	Br	PPh$_3$	82%
p-Anisyl	Br	PPh$_3$	74%
2-Pyridyl	Br	PPh$_3$	76%
2-Thienyl	Br	PPh$_3$	64%
p-Acetophenyl	Cl	PPh$_3$	29%
p-Acetophenyl	Cl	P(Cy)$_2$(*o*-biphenyl)	47%
p-Tolyl	Cl	P(Cy)$_2$(*o*-biphenyl)	63%
p-Anisyl	Cl	P(Cy)$_2$(*o*-biphenyl)	71%

Figure 1.29: Improved siloxane cross-couplings

Nolan has also demonstrated that aryl chlorides and bromides are appropriate coupling partners when nucleophilic imidazolium carbenes are employed as the ligand.[69]

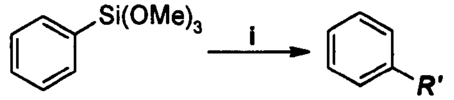


Reagents and conditions: i) Ph-Si(OMe)$_3$, Pd(OAc)$_2$, IPr·HCl, TBAF, 1,4-dioxane/THF, 80°C.

R	Halide	Time	Yield
p-Tolyl	Br	6h	93%
p-Acetophenyl	Br	1h	100%
2-Pyridyl	Br	7h	81%
p-Anisyl	Cl	17h	19%
p-Tolyl	Cl	4h	29%
p-Acetophenyl	Cl	3h	100%
p-Cyano	Cl	2h	100%

Figure 1.30: Siloxane cross-coupling with imidazolium carbene co-catalyst

Most recently, Fu has shown that aryl trisiloxanes can undergo cross-coupling with *alkyl* bromides using PdBr$_2$/P(t-Bu)$_2$Me as catalyst and TBAF as fluoride source.[70]



Reagents and conditions: i) alkyl bromide, $PdBr_2$, $P(t\text{-}Bu)_2Me$, TBAF, rt.

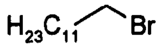
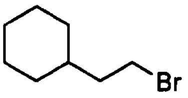
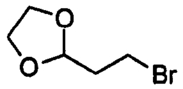
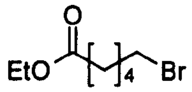
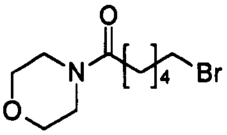
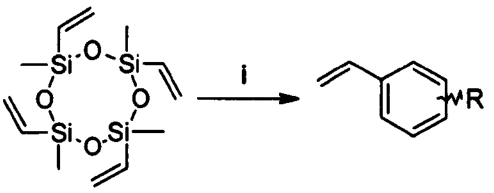
Alkyl bromide	Yield
	75
	81%
	71%
	79%
	73%

Figure 1.31: Alkylation of aryl siloxanes

Denmark has demonstrated that commercially available vinylpolysiloxane can be cross-coupled with aryl and alkenyl halides.[71] Polysiloxanes are attractive coupling partners from an industrial perspective as several polyalkenylsiloxanes are inexpensive items of commerce.



Reagents and conditions: i) aryl iodide, Pd(dba)$_2$, TBAF, THF, rt.

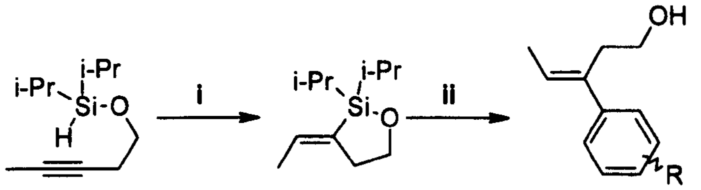
Aryl iodide	Yield
p-Acetophenyl	88%
p-Anisyl[(a)]	63%
m-Nitro	87%
m-Benzyl alcohol	59%
o-Methyl benzoate	83%
1-Naphthyl	64%

(a) AsPh$_3$ added

Figure 1.32: Vinylation of aryl iodides using polysiloxanes

DeShong[72] and Masuda[73,74] have demonstrated that aryl and alkenyl trisiloxane cross-coupling substrates can be readily prepared from commercial trialkoxysilanes *via* palladium catalysed coupling with aryl halides. One drawback with this is that the reaction usually works poorly for electron deficient aryl substrates. Masuda has also recently shown [Rh(cod)(MeCN)$_2$]BF$_4$ to be effective for the coupling of electron deficient aryl halides and triethoxysilanes.[75]

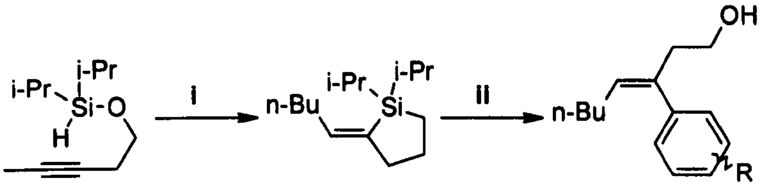
Denmark has explored the synthetic utility of siloxane-based cross-coupling as a powerful method for the preparation of stereodefined trisubstituted alkenes from propargylic alcohols *via* intramolecular *syn*[76-78] and *anti*[78,79] hydrosilylation protocols.



Reagents and conditions: i) $H_2PtCl_6 \cdot 6H_2O$, CH_2Cl_2, 83%; ii) aryl iodide, $Pd(dba)_2$, TBAF, THF.

Aryl iodide	Temperature	Yield
Phenyl	rt	88%
p-Anisyl	rt	72%
p-Acetophenyl	rt	70%
m-Benzyl alcohol	rt	81%
o-Anisyl	35°C	74%
p-Ethyl benzoate	45°C	86%

Figure 1.33: Intramolecular *syn*-hydrosilylation/cross-coupling

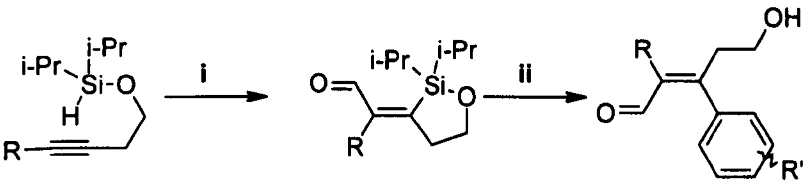


Reagents and conditions: i) $[(C_6H_6)RuCl_2]_2$, CH_2Cl_2, 40°C, 86%; ii) aryl iodide, $Pd(dba)_2$, TBAF, THF.

Aryl iodide	Temperature	Yield
Phenyl	45°C	65%
p-Anisyl	rt	60%
p-Acetophenyl	rt	66%
m-Benzyl alcohol	rt	59%
o-Anisyl	rt	68%
p-Ethyl benzoate	40°C	72%

Figure 1.34: Intramolecular *anti*-hydrosilylation/cross-coupling

In addition to hydrosilylation, it is also possible to carry out formylsilylation with homopropargylic alcohols. Cross-coupling of the resulting siloxanes gives highly substituted α,β-unsaturated aldehydes.[80] Interestingly, cross-coupling of this type of electron deficient alkenyl siloxane requires the use of copper iodide and a hydrosilane as co-catalysts.



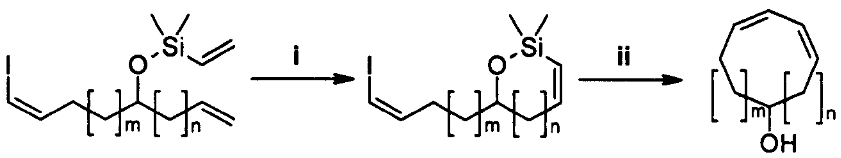
Reagents and conditions: i) [Rh(t-BuCN)$_4$][Co(CO)$_4$], CO 150psi, toluene, 70°C, 72% for both R = H and R = Me; ii) aryl iodide, APC dimer, CuI, KF·2H$_2$O, methylhydrocyclosiloxane, DMF, rt.

R	i) Yield	Aryl iodide	ii) Yield
H	72%	Phenyl	93%
H		*p*-Anisyl	87%
H		*p*-Acetophenyl	91%
H		*o*-Tolyl[(a)]	79%
Me	72%	*p*-Acetophenyl	83%

(a) Increased quantities of siloxane and KF·2H$_2$O required

Figure 1.35 Silylformylation and cross-coupling

Cyclic alkenyl siloxanes can also be synthesised using ring closing metathesis.[81] This approach has been used to synthesise medium sized rings containing 1,3-*cis-cis* dienes,[82]



Reagents and conditions: i) Schrock's molybdenum catalyst, benzene, rt; ii) APC dimer, TBAF, THF, rt, 45-75min.

m,n	**Ring size**	**RCM yield**	**Cross-coupling yield**
1,1	8	83%	60%(a)
2,1	9	81%	70%
3,1	10	82%	63%
4,1	11	81%	55%
5,1	12	83%	72%
2,2	10	80%	71%

(a) 1:1 mixture of 7 and 8 membered rings

Figure 1.36: RCM/cross-coupling formation of medium sized cyclic 1,3-dienes

Formation of the cyclic octadiene (m,n = 1,1) did not proceed smoothly, and the 7-membered *cine* rearrangement product was also observed in addition to the desired *cis-cis* 8 membered diene.

This protocol was also applied to the total synthesis of the antifeedant natural product (+)-brasilenyne.[83]

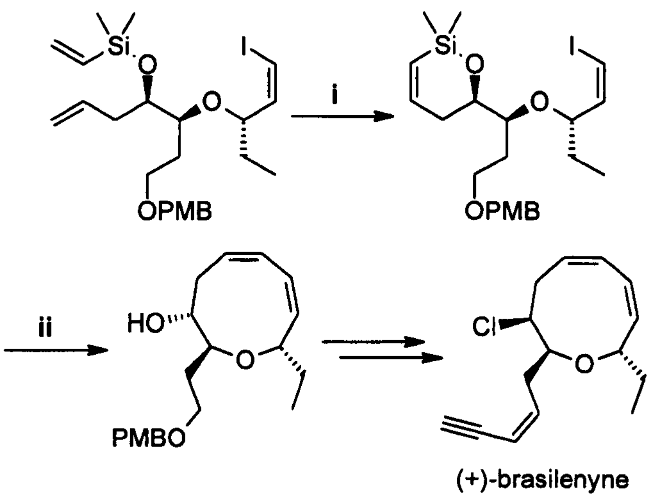
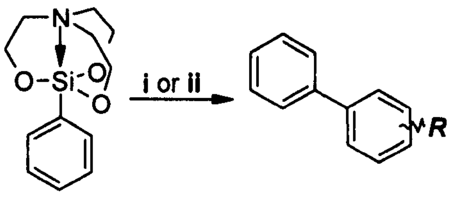


Figure 1.37 Synthesis of (+)-brasilenyne *via* RCM/cross-coupling protocol

Reagents and conditions: i) Schrock's molybdenum catalyst, benzene, rt, 92%; ii) APC dimer, TBAF, benzene, 60°C, 61%.

1.3.3 Silatranes

The coupling of siloxanes with aryl triflates is an inefficient reaction, usually resulting in hydrolysis of the triflate rather than oxidative addition. In an attempt to address this limitation DeShong has utilised silatranes as coupling partners with aryl triflates.[84] Unlike Vedejs' carbastannatrane (figure 1.6), or Kosugi's carbagermatrane (figure 1.66), DeShong found that silatrane was not sufficiently hypervalent to cross-couple and required the presence of intermolecular fluoride for a successful reaction to take place (*cf.* Faller's germatrane, figure 1.68).



Reagents and conditions: i) aryl triflate, TBAF·20H_2O, Pd(dba)$_2$, P(Cy)$_2$(*o*-biphenyl), THF, 60°C, 12h; ii) aryl halide, TBAF, Pd(OAc)$_2$, PPh_3, THF, 60°C.

(Pseudo)halide	R	Yield
OTf	*p*-Anisyl	90%
OTf	*o*-Anisyl	90%
OTf	Phenyl	75%
OTf	*p*-Tolyl	87%
Br	*p*-Acetophenyl	71%
Br	*p*-Anisyl	73%
I	*p*-Acetophenyl	80%

Figure 1.38: DeShong's silatrane cross-couplings

The use of TBAF with 20 equivalents of water is required to avoid hydrolysis of the triflate. The use of silatranes is advantageous when coupling triflates as the alkoxide leaving group expelled as a result of the attack of fluoride at silicon remains tethered to the silicon centre and is less available to hydrolyse the triflate.

1.3.4 Silacyclobutanes (siletanes):

During the mid 1990's Denmark's lab reported on the enhanced Lewis acidity of silacyclobutanes relative to simple trialkylsilanes in Mukaiyama-type aldol addition reactions.[85,86] This enhancement was attributed to the strain release on going from a tetra- to a penta-coordinate species.

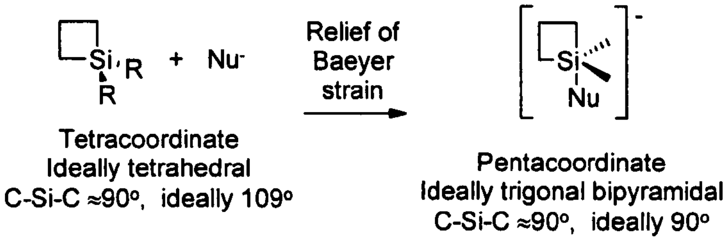
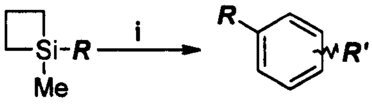


Figure 1.39: Strain release Lewis acidity

In 1999 Denmark, in pursuit of reactive silanes that would be more versatile than halosilanes and siloxanes, reported the successful cross-coupling of *cis*- and *trans*-alkenyl methylsilacyclobutanes with aryl iodides.[87,88] The reactions worked well for both electron deficient and electron rich aryl iodides and proceeded with almost complete retention of configuration for substituted alkenes. *E*-alkenylsilacyclobutanes were synthesised *via* reduction of an alkyne with DIBAL, followed by quenching with 1-chloro-1-methylsilacyclobutane. The *Z*-alkene isomers were prepared by reduction of the corresponding 1-alkynyl-1-methylsilacyclobutane with DIBAL.[87]

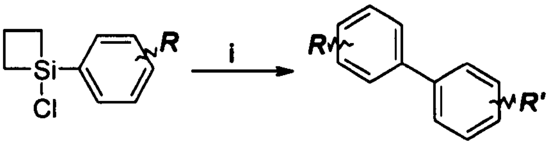


Reagents and conditions: i) aryl iodide, Pd(dba)$_2$, TBAF, THF, rt.

Arylsilane: ***R***	Aryl Iodide: ***R'***	Yield (%)	Product E/Z ratio
E-Hept-1-enyl	*p*-Acetophenyl	84	99.7/0.3
Z-Hept-1-enyl	*p*-Acetophenyl	88	2.0/98.0
Vinyl	*p*-Acetophenyl	85	-
2-Propenyl	*p*-Acetophenyl	89	-

Figure 1.40 Silacyclobutane cross-coupling

Although *methyl*silacyclobutanes proved to be too unreactive to effectively transfer aryl groups, the analogous aryl *halo*silacyclobutanes proved to be sufficiently activated to allow smooth formation of biaryls.[89]



Reagents and conditions: i) aryl iodide, APC dimer, P(t-Bu)$_3$, TBAF, THF, 65°C.

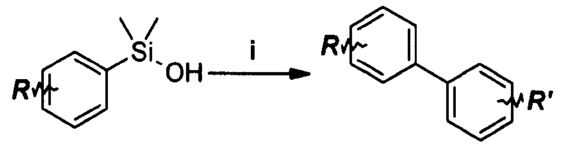
Arylsilane: ***R***	Aryl Iodide: ***R'***	Yield (%)
p-Anisyl	Phenyl	91%
p-Anisyl	*p*-Acetophenyl	73%
p-Anisyl	1-Naphthyl	85%
p-Anisyl	*m*-Nitro	0%[a]
p-Anisyl	*o*-Tolyl	89%
p-Anisyl	*m*-Pyridyl	71%
o-Tolyl	*m*-Tolyl	76%
o-Tolyl	*o*-Nitro	77%

Figure 1.41 Arylsilacyclobutane cross-coupling

Arylchlorosilacyclobutanes were synthesised from the reaction of dichlorosilacyclobutane with the appropriate organometallic reagent. Conversion of the chlorides to arylfluorosilacyclobutanes was accomplished with CuF$_2$.[89]

1.3.5 Silanols

The use of silanols as coupling reagents was first demonstrated by Hiyama in 1999 when cross-coupling aryl monosilanols with aryl iodides using silver(I) oxide as an activator.[90]

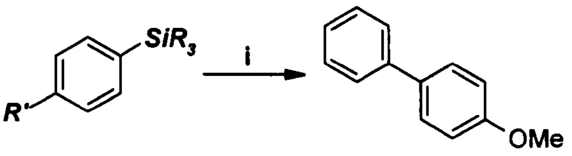


Reagents and conditions: i) aryl iodide, $Pd(PPh_3)_4$, Ag_2O, THF, 60°C.

Arylsilanol: *R*	**Aryl iodide: *R'***	**Yield (%)**
p-Anisyl	Phenyl	80%
p-Anisyl	*o*-Tolyl	67%
p-Anisyl	*p*-Acetophenyl	50%
p-Trifluoromethyl	*p*-Anisyl	84%
o-Tolyl	*p*-Anisyl	30%

Figure 1.42: Hiyama's cross-coupling of arylmonosilanols with Ag_2O activator

Hiyama later demonstrated that di- and trisilanols could also couple in good yields and under milder reaction conditions or shorter reaction times.[91] In these further studies Hiyama showed that the silver(I) oxide activator underwent chemical change and was converted to silver(I) iodide during the course of the reaction. This indicated that the silver salt was not only activating the silanol but was also interacting with the arylpalladium(II) iodide intermediate. The unreactivity of trimethylsilane and pentamethyldisiloxane analogues was suggested to implicate the hydroxy group(s) as also having a crucial role in the reaction mechanism.



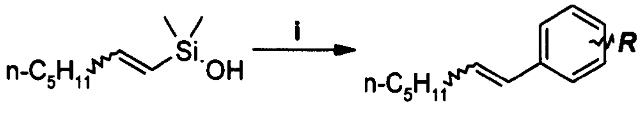
Reagents and conditions: i) aryl iodide, Pd(PPh$_3$)$_4$, Ag$_2$O, THF, 60°C.

Arylsilane	SiR$_3$	Aryl iodide	Time (h)	Yield
p-Anisyl	SiMe$_3$	Phenyl	36	0%
p-Anisyl	SiMe$_2$OSiMe$_3$	Phenyl	36	4%
p-Anisyl	SiMe$_2$OH	Phenyl	36	80%
p-Anisyl	SiEt(OH)$_2$	Phenyl	12	95%
Phenyl	SiEt(OH)$_2$	*p*-Anisyl	12	95%
Phenyl	Si(OH)$_3$[a]	*p*-Anisyl	12	83%

(a) Silanetriol most likely present as an unpurified mixture of trisiloxanes

Figure 1.43: Cross-coupling of arylsilanols

In 2000 Denmark carried out similar reactions coupling alkenyl monosilanols with aryl iodides in excellent yields with little isomerisation of the alkene geometry.[92,93]

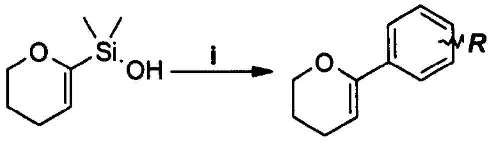


Reagents and conditions: i) aryl iodide, Pd(dba)$_2$, TBAF, THF, rt.

Alkene geometry	Aryl iodide	Time (min)	Yield	*E*/*Z* ratio
E	Phenyl	10	91%	97.8/2.2
Z	Phenyl	10	90%	2.7/97.3
E	2-Thienyl	180	83%	95.7/4.3
Z	2-Thienyl	180	81%	2.5/97.5
E	*p*-Acetophenyl	10	93%	96.5/3.5
Z	*p*-Acetophenyl	10	92%	4.8/95.2
E	*p*-Anisyl	10	95%	97.2/2.8
Z	*p*-Anisyl	10	94%	2.6/97.4

Figure 1.44:Alkenyl silanol cross-coupling

Denmark also demonstrated the coupling of α-alkoxyalkenylsilanols in the presence of TBAF.[94]



Reagents and conditions: i) aryl iodide, APC dimer, TBAF, THF, rt.

R	Time (min)	Yield (%)
p-Ethyl benzoate	10	84%
o-Methyl benzoate	240	92%
o-Anisyl	10	74%
m-CH_2OAc	20	87%

Figure 1.45: Cross-coupling of α-alkoxyalkenylsilanols

Alkynyl monosilanols were shown to be competent substrates for this type of cross-coupling.[95]

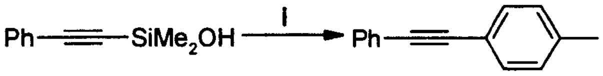


Figure 1.46: Alkynylsilanol cross-coupling

Reagents and conditions: 4-iodotoluene, $Pd(PPh_3)_4$, TBAF, THF, 60°C, 99%.

It was at this point in time that detailed mechanistic work by Denmark revealed an unforeseen commonality between the silacyclobutane, siloxane and silanol based coupling protocols: they all react *via* a common intermediate in the presence of TBAF in THF/H_2O. Using careful ^{29}Si and ^{19}F NMR analysis this intermediate was identified as being a silanol with a hydrogen-bonded fluoride adduct.[96] The fact that the rate of these reactions is second order in regard to the silanol concentration led Denmark to suggest that this intermediate probably dimerises prior to transfer of the alkenyl group to palladium.[85]

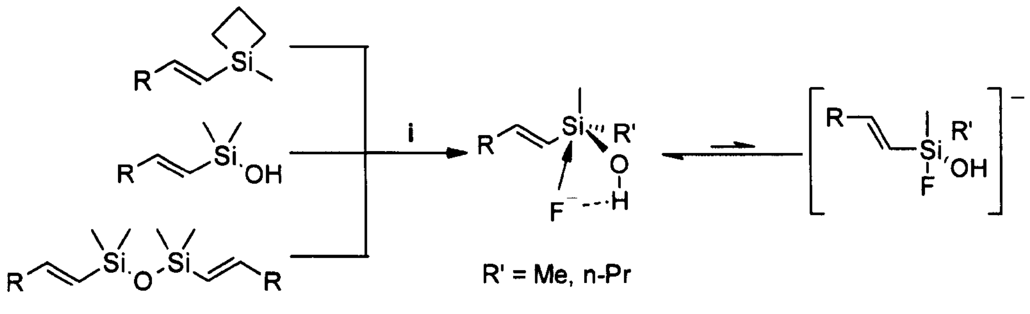
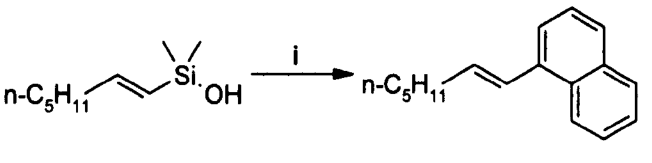


Figure 1.47: Reaction of silacyclobutanes, silanols and disiloxanes with TBAF

Reagents and conditions: i) TBAF, H_2O, THF, rt.

Following this intriguing discovery, Denmark went on to carry out alkenyl- and aryl silanol cross-couplings using bases as activators in place of fluoride. Sodium hydride, potassium trimethylsilanolate,[97] and cesium carbonate[98] were all shown to be viable alternatives to fluoride. These protocols are valuable synthetically because they allow cross-coupling to be carried out in complex molecules that are sensitive to fluoride ions, for example those containing certain silyl ether protecting groups.



Reagents and conditions: i) 1-iodonaphthalene, $Pd(dba)_2$, activator, DME, 60°C.

Activator	Time (min)	Yield
MeLi	1440	0%
NaH	60	81%
KH	15	82%
KOt-Bu	180	90%
$KOSiMe_3$	120	93%

Figure 1.48: Alkenyl silanol cross-coupling

Whereas fluoride most likely activates silanes *via* a hydrogen-bonded silanol-fluoride adduct leading to a pentavalent silicate species (*vide infra*), Denmark proposed that bases activate the silanol by forming a silanolate anion which, in addition to dimerising to form a hypervalent silicate, is also capable of coordinating to the arylpalladium(II) halide, thereby rendering the rate determining transmetallation step intramolecular.[85]

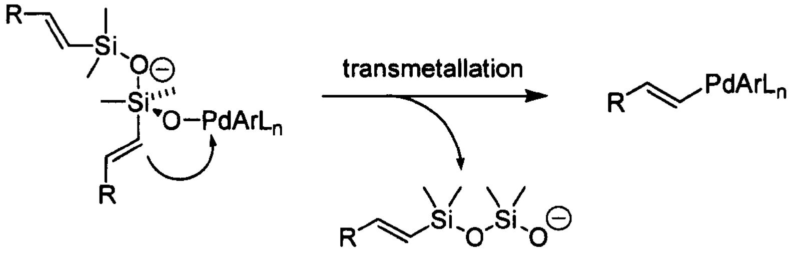


Figure 1.49: Proposed transmetallation mechanism for base mediated silanol cross-coupling

Synthesis of silanols has generally been carried out by hydrolysis of the corresponding chlorosilanes,[91] or by lithiation of an appropriate alkenyl or aryl halide followed by quenching with hexamethylcyclotrisiloxane.[92] Denmark has recently described a much milder synthesis of arylmonosilanols *via* the palladium catalysed coupling of arylbromides with 1,2-diethoxy-1,1,2,2-tetramethyldisilane, followed by mild hydrolysis using an AcOH/NH_4OAc buffer at pH 5.6.[99]

1.3.6 Safety-catch silanes

The previously described work involving halosilanes, siloxanes and silanols has firmly established organosilane cross-coupling as a viable rival to Suzuki and Stille couplings for simple substrates. However, alkenyl- and aryl heterosilanes are both reactive and labile, even to atmospheric conditions, and as a result are difficult to handle; more so even than the corresponding boronic acids or esters. This makes them unsuitable for carrying through even relatively simple synthetic sequences and will limit their applicability to the total synthesis of complex, multifunctional organic molecules. Consequently, one of the most recent and significant developments in the organosilane cross-coupling arena has been the advent of "safety-catch" silanols.

Safety-catch silanols are ideally stable to a wide range of reaction conditions, easy to handle and stable to moisture and chromatography, but possess a moiety that can be selectively unmasked or "activated" under specific conditions to reveal a reactive silanol functionality.

The requirements for a useful safety-catch silanol are similar to those for silane precursors for Fleming-Tamao oxidation (the fluoride promoted oxidation of alkylsilanes to alkyl alcohols by hydrogen peroxide) for which various ingenious safety-catch strategies have already been devised.[100,101] Indeed, the requirements placed on the silicon centre to allow Fleming-Tamao oxidation to proceed appear to be similar to those for cross-coupling; namely that a heteroatom substituent on silicon is necessary for initial coordination of fluoride to give a pentavalent intermediate.[100,101] A significant difference is that safety-catch silanes for Fleming-Tamao oxidation liberate *alkyl*heteroatom-substituted silanes rather than *alkenyl-* or *aryl*heteroatom-substituted silanes (*e.g.* silanols). This requirement either rules out or limits the scope of many of the Fleming-Tamao safety catch silanes for application in cross-coupling where frequently an aryl or alkenyl group is in fact selectively removed from silicon in preference to the alkyl group to be oxidised.[100,101]

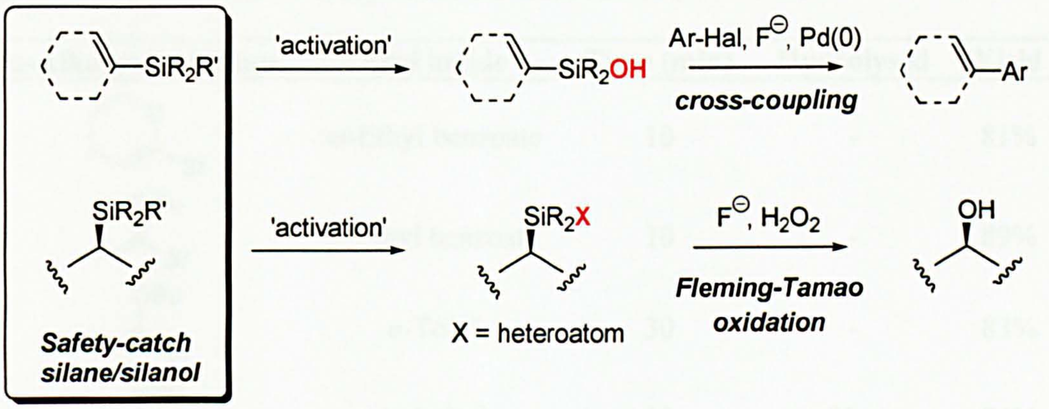
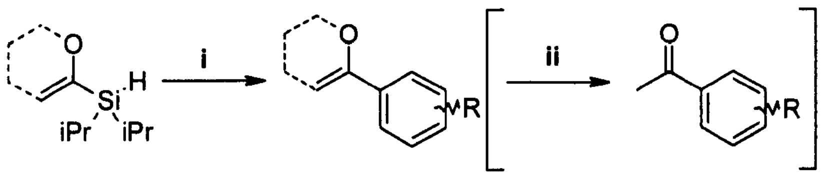


Figure 1.50: Comparison of Fleming-Tamao oxidation requirements with silane cross-coupling requirements

The methylsilacyclobutanes developed by Denmark (*vide supra*) can be considered to constitute the first safety-catch silanols described for cross-coupling. Methylsilacyclobutanes are, however, restricted to the transfer of simple alkenyl groups and the strain inherent in the four-membered ring makes them rather labile compounds. More versatile examples of safety-catch silanols that have been subsequently described are:

Silyl Hydrides: These derivatives were first reported as viable cross-coupling substrates by Denmark in 2000. Silyl hydrides were shown to transfer α-alkoxyalkenyl groups to aryl iodides in good yields using TBAF in THF.[94] It was proposed that the hydrides were converted to silanols, *in situ*, by fluoride catalysed oxidative hydrolysis. Indeed, evolution of a gas was observed on mixing the hydrides with TBAF in THF/H_2O. Since silyl hydrides are generally stable to flash chromatography they are attractive coupling precursors. However, the scope and limitations of these derivatives as coupling partners has yet to be fully explored.



Reagents and conditions: i) aryl iodide, TBAF, THF, rt; ii) 1N HCl.

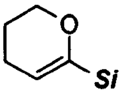
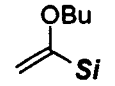
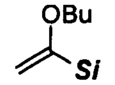
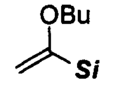
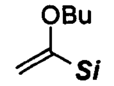
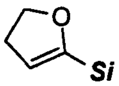
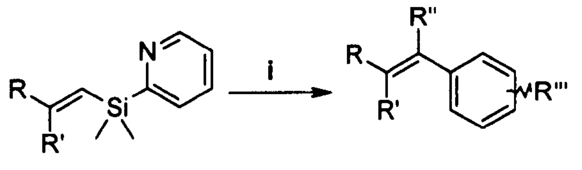
α-Alkoxyvinyl silane	Aryl iodide	Time (min)	Hydrolysed	Yield
	*m*-Ethyl benzoate	10	-	81%
	*p*-Ethyl benzoate	10	-	89%
	*o*-Tolyl	30	-	83%
	*p*-Anisyl	10	Yes	94%
	*o*-Cyano	900	-	76%
	*p*-Acetophenyl	10	-	71%

Figure 1.51: Cross-coupling reactivity of α-alkoxyvinyl silyl hydrides

2-Pyridylsilanes: In 2001 Yoshida utilised a dimethyl(2-pyridyl)silyl moiety to cross-couple alkenyl groups with aryl- and heteroaryl iodides in the presence of TBAF/H_2O. ^1H NMR was used to monitor the reaction of 2-pyridylsilane with commercially available TBAF at rt in d_8-THF. This revealed that the alkenyl 2-pyridyl silane underwent selective nucleophilic *ipso*-desilylation to remove the pyridine ring and consequently form an alkenylsilanol *in situ.*[102-104] The precursors were stereodefined trisubstituted alkenylsilanes, prepared by Heck-type coupling reactions of vinyldimethyl(2-pyridyl)silane with aryl iodides. During the Heck coupling the 2-pyridylsilyl group was proposed to coordinate to the palladium, thereby facilitating delivery of the alkenyl group for carbopalladation. This combination of Heck and cross-coupling chemistry allowed the synthesis of tri-substituted alkenes, but could not access tetra-substituted alkenes.

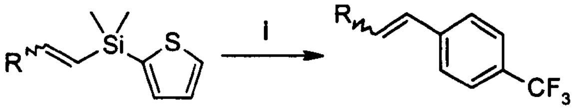


Reagents and conditions: i) Aryl iodide, $PdCl_2(PhCN)_2$, TBAF, THF, 60°C.

R	R'	R''	Aryl iodide	Yield
n-Bu	H	H	H	99%
p-Tolyl	H	H	*p*-Formyl	91%
2-Thienyl	H	H	*p*-Acetophenyl	100%
m-Pyridyl	H	H	*o*-Tolyl	97%
Phenyl	H	Phenyl	*p*-Acetophenyl	57%
3-Thienyl	H	Phenyl	*p*-Ethyl benzoate	71%
Phenyl	Phenyl	H	*p*-Acetophenyl	75%
2-Thienyl	Phenyl	H	*m*-Formyl	84%
Phenyl	3-Thienyl	H	*p*-Ethyl benzoate	100%

Figure 1.52: Cross-coupling of alkenyl 2-pyridyl silanes

2-Thienylsilanes: Hiyama has accessed alkenyldimethyl(2-thienyl)silanes *via* the stereoselective hydrosilylation of alkynes with dimethyl(2-thienyl)silane, and has observed that they can be selectively activated by TBAF/H_2O, again with ^1H NMR evidence for nucleophilic *ipso*-desilylation of the thienyl ring.[105] Alkenyl dimethylsilanol formation occurs under milder conditions than required when employing the corresponding 2-pyridylsilanes. 2-Thienylsilanes have previously been employed as safety-catch silanes in the context of Fleming-Tamao oxidation.[100,101]

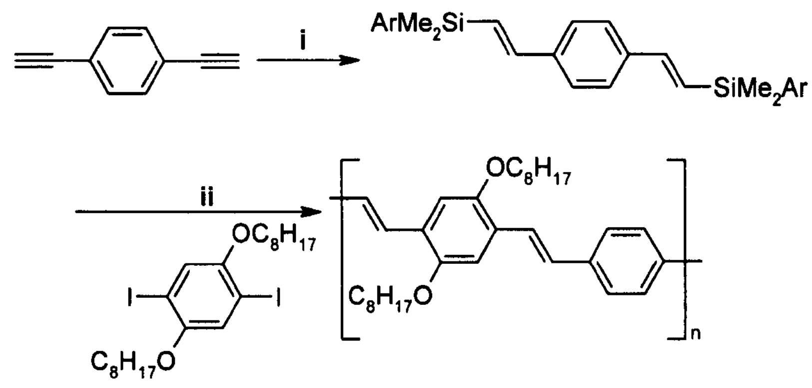


Reagents and conditions: i) aryl halide, Pd(OAc)$_2$, TBAF, THF, rt.

R	Aryl halide	Time	Yield
E-Hexyl	*p*-Iodo trifluoromethyl	1h	100%
E-Hexyl	*p*-Iodo anisole	30min	97%
E-Hexyl	Iodo *p*-Ethyl benzoate	30min	94%
E-Hexyl	*p*-Bromo trifluoromethyl	5h	96%
Z-Hexyl	*p*-Iodo trifluoromethyl	1h	98%
H	*p*-Iodo trifluoromethyl	30min	90%
Phenyl	*p*-Iodo trifluoromethyl	1h	98%
Trimethylsilyl	*p*-Iodo trifluoromethyl	1h	95%

Figure 1.53: Cross-coupling of alkenyl 2-thienyl silanes

2-Thienylsilanes and (3,5-bistrifluoromethylphenyl)dimethylsilanes have been employed in the synthesis of poly(*p*-phenylenevinylene)s.[106,107]



Reagents and conditions: i) $RuHCl(CO)(PPh_3)_3$, $HSiMe_2Ar$, CH_2Cl_2, rt, 1h; ii) APC dimer, $TBAF{\cdot}3H_2O$, THF.

Aryl	i) Yield	ii) Yield	ii) M_n (M_w/M_n)
2-Thienyl	75% [(*E*/*E*)/(*E*/*Z*)] >99/1	99%	5300 (1.62)
3,5-bistrifluoromethylphenyl	89% [(*E*/*E*)/(*E*/*Z*)] =99/1	99%	6300 (2.30)

Figure 1.54: Use of thienylsilanes and (3,5-bistrifluoromethylphenyl)silanes in cross-coupling

The precise mechanism for the transformation with (3,5-bistrifluoromethylphenyl)dimethylsilanes is unclear, as Katayama presents no information relating to the intermediate formed. However it seems plausible that the 3,5-bistrifluoromethylphenyl group is masking a silanol. A further possibility is that it is also increasing the Lewis acidity of the silicon centre, thereby activating it towards the coordination of fluoride.

Dimethylphenylsilanes: The dimethylphenylsilyl group is the prototypical safety-catch silane for Fleming-Tamao oxidation, as introduced and popularised primarily by Fleming himself.[100,101] In this context alkyl dimethylphenylsilanes are readily prepared by a wide range of methods, they are stable to a wide variety of reaction conditions, and activation is usually achieved by *electrophilic ipso*-desilylation of the phenyl group using *e.g.* TFA/KHF_2, $HBF_4{\cdot}Et_2O$, $BF_3{\cdot}2AcOH$, Br_2, KBr/AcOOH, ICl, $Hg(OAc)_2$, or $Hg(OTFA)_2$.[100,101]

The dimethylphenyl group is also easily appended to alkenyl moieties and Anderson has shown that this group is a viable safety-catch silanol for cross-coupling of alkenyl groups.[108] Electrophilic activation is not applicable in this context because the alkene would undergo *ipso*-desilylation in preference to the phenyl group. However, *nucleophilic* activation using potassium *tert*-butoxide in the presence of 18-crown-6 was shown to display selectivity for *ipso*-desilylation of the phenyl ring, liberating the requisite alkenyl silanols exclusively. These silanols were found to cross-couple efficiently with iodobenzene under Denmark's conditions although, interestingly, the major products were those of *cine* substitution, suggestive of either a Heck-type mechanism or reaction *via* a Pd(0)-carbene intermediate.[108]

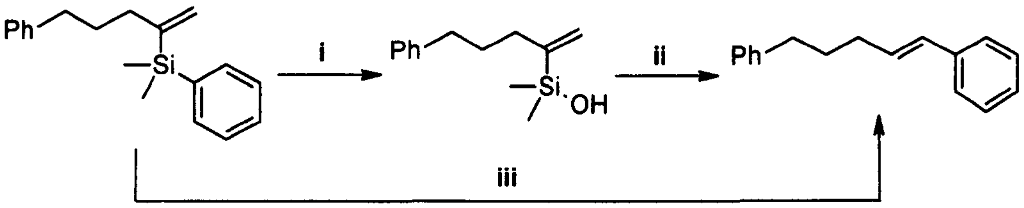
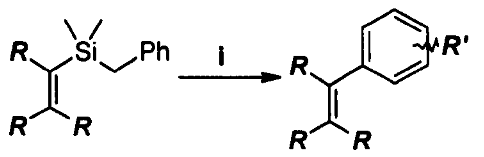


Figure 1.55: Anderson's coupling of a phenyldimethylsilane

Reagents and conditions: i) t-BuOK, 18-c-6, TBAF, undried THF, rt, 2h, 76%; ii) iodobenzene, $Pd_2(dba)_3$, TBAF, undried THF, rt, 30min, 89%; iii) t-BuOK, 18-c-6, TBAF, iodobenzene, $Pd_2(dba)_3$, undried THF, rt, 45min, 85%.

The robust nature of the dimethylphenylsilyl moiety and the reasonably mild activation conditions make this approach very appealing from a synthetic standpoint. However, the scope of this type of safety-catch silanol remains to be delineated particularly with respect to the level of selectivity that can be achieved during activation when employing a more diverse set of alkenyl and aryl substrates.

Dimethylbenzylsilanes: A very recently described safety-catch silane for cross-coupling is the dimethylbenzyl group as introduced by Trost.[109] Dimethylbenzylsilyl substituted alkenes can be accessed *via* hydrosilylation of alkynes or a silyl-alkyne Alder ene reaction.



Reagents and conditions: i) organic iodide, $Pd_2(dba)_3 \cdot CHCl_3$, TBAF, THF, 0°C 10min, rt <4h.

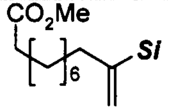
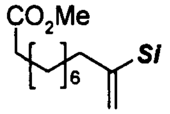
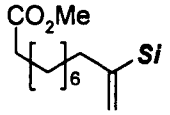
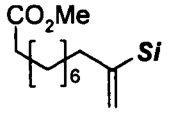
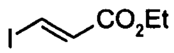
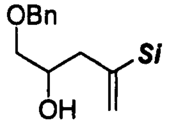
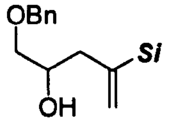
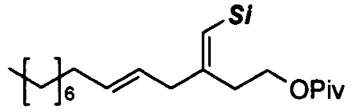
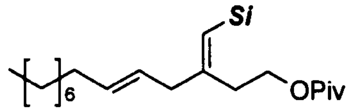
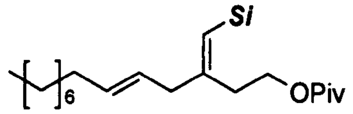
α-Alkoxyvinyl silane	Aryl iodide	Yield
	Phenyl	97%
	*p*-Acetophenyl	89%
	*m*-Pyridyl	78%
		65%
	Phenyl	95%
	*o*-Tolyl	91%
	*p*-Acetophenyl	91%
	*m*-Cyano	92%
	*m*-Anisyl	60%

Figure 1.56: Cross-coupling of benzylsilanes

The dimethylbenzylsilane appears to be the most reactive of the safety-catch silanes disclosed thus far, as it releases a silanol after just 10 minutes at 0°C in the presence of TBAF. This reactivity is neatly complemented by the stability of dimethylbenzylsilanes towards mild acids, bases, and buffered fluoride solutions.[109]

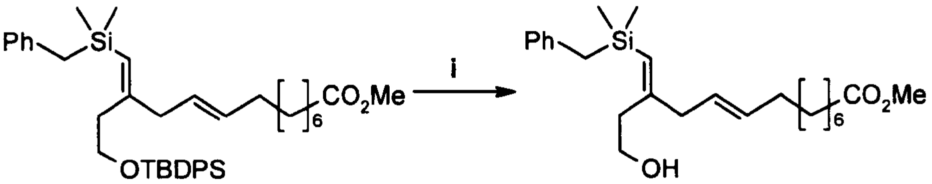
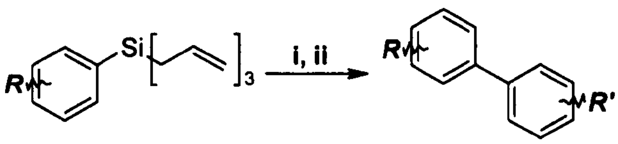


Figure 1.57: Stability of benzylsilanes towards buffered fluoride

Reagents and conditions: i) TBAF, AcOH, DMF aq, rt, 24h, 83%.

Triallylsilanes: More recently still, Hiyama has shown the ability of aryltriallylsilanes to undergo cross-coupling.[110]



Reagents and conditions: i) TBAF, DMSO/H_2O (10/1), rt, 1h; ii) aryl bromide, $PdCl_2$, PCy_3, 80°C.

R	R'	Time	Yield
H	*p*-Trifluoromethyl	3h	95%
H	*p*-Nitro	3h	87%
H	*p*-Anisyl	3h	92%
H	*o*-Biphenyl	3h	98%
H	1-Naphthalene	3h	96%
H	*m*-Benzothiophenyl	5h	93%
p-Anisyl	*p*-Ethyl benzoate	1h	72%
p-Trifluoromethyl	*p*-Ethyl benzoate	1h	49%
o-Tolyl	*p*-Ethyl benzoate	1h	57%

Figure 1.58: Cross-coupling of aryltriallylsilanes

Aryldiallylmethylsilanes and arylallyldimethylsilanes do not undergo coupling under these conditions, although Hiyama has shown that phenylallyldimethylsilane is converted to a mixture of phenyldimethylsilanol and diphenyltetramethyldisiloxane by the action of TBAF in DMSO/H_2O. He has not been able to elucidate the product

---

obtained when phenyltriallylsilane is exposed to fluoride, although it seems likely that these couplings also proceed *via* a silanol or siloxane intermediate resulting from the cleavage of allyl groups by fluoride.

1.4 Mechanism of organosilane cross-couplings

The reactions of organosilanes and organogermanes with unsaturated (pseudo)halides, catalysed by Pd(0), are generally regarded as proceeding *via* a mechanism similar to that proposed for the Stille reaction of organostannanes (*vide supra*).

For Stille cross-coupling of organostannanes, judicious choice of ligand/palladium source, solvent and temperature are generally sufficient to allow for an efficient catalytic process (although fluoride salts are sometimes added in specific circumstances, *vide supra*). For organosilanes and organogermanes, it is apparent from the foregoing survey that the inclusion of a nucleophilic activator such as fluoride is generally essential. Clearly, the additive further modulates the reactivity of the intermediates in the catalytic cycle, but a consensus has yet to emerge as to the relevance and relative importance of various mechanisms by which this modulation might be achieved. The following discussion focuses on the possible interactions of fluoride salts with the reactive intermediates that participate in the rate determining transmetallation step, *i.e.* the aryl Pd(II) halide species and the group 14 organometallic species. As most available data pertains to organosilanes, the possible interactions are introduced in this context before briefly considering likely similarities and differences for organogermanes and germatrane-type reactants.

1.4.1 Interactions of fluoride salts with the aryl Pd(II) halide intermediate

Fluoride ions can participate in halide exchange with the initially formed aryl Pd(II) halide intermediate. As the result of the higher electronegativity of fluorine relative to the other halides, the resulting aryl Pd(II) fluoride might be expected to be more electrophilic at palladium and hence more reactive towards transmetallation. However, aryl Pd(II) fluorides have been reported to be rather inert relative to the corresponding iodides, bromides, and chlorides.[111] In contrast, aryl Pd(II) *hydroxides* are known to be highly active towards transmetallation, at least in Suzuki cross-coupling of boronic acids, where their high reactivity has been suggested to accrue from their ability to coordinate to boronic acids, forming boronic "ate" complexes and rendering the subsequent transmetallation *intra*molecular.[112,113] This is significant because most fluoride salts, such as TBAF, contain water of crystallisation and are extremely difficult to obtain and use in anhydrous form. Ligand exchange at palladium of the halide by hydroxide associated with the hydrated fluorides could occur under most of the conditions used for cross-coupling with these activators.

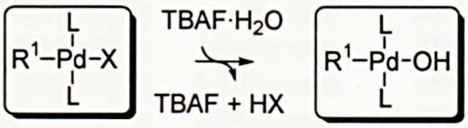


Figure 1.59: Proposed formation of aryl palladium(II) hydroxides

This might allow a similar intramolecular transmetallation pathway as proposed for Suzuki reactions to operate.

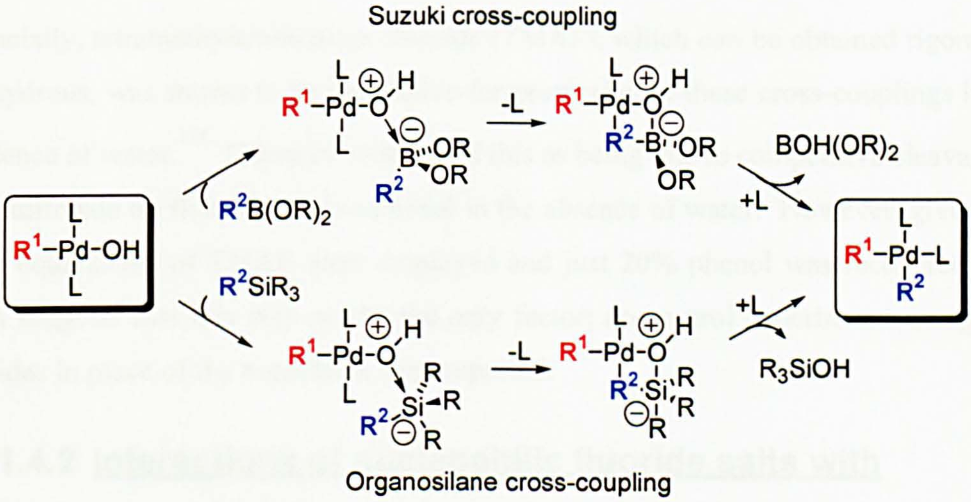
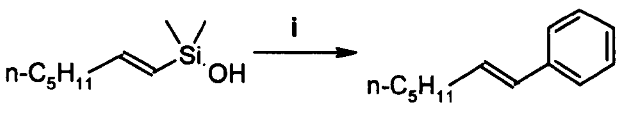


Figure 1.60: Potential commonality between cross-coupling transmetallation of organoboranes and organosilanes

In support of this hypothesis, Denmark has shown that water is a critical additive in fluoride promoted reactions of alkenylsilanols with perfluorobutylsulfonylbenzene (phenyl nonaflate, PhONf).[114]



Reagents and conditions: i) phenyl nonaflate, $PdCl_2$, $P(t\text{-}Bu)_2$(2-biphenyl), fluoride, solvent, rt.

Fluoride	Solvent	Yield
$TBAF{\cdot}3H_2O$	1,4-dioxane	40%
$TBAF{\cdot}4H_2O$	1,4-dioxane	71%
$TBAF{\cdot}6H_2O$	1,4-dioxane	95%
$TBAF{\cdot}8H_2O$	1,4-dioxane	89%
$TBAF{\cdot}10H_2O$	1,4-dioxane	76%
TMAF	DMF	1%
$TMAF{\cdot}4H_2O$	DMF	95%
$TMAF{\cdot}6H_2O$	DMF	99%
$TMAF{\cdot}8H_2O$	DMF	83%

Figure 1.61: Effect of water additive on cross-coupling

Crucially, tetramethylammonium fluoride (TMAF), which *can* be obtained rigorously anhydrous, was shown to be ineffective for promotion of these cross-couplings in the absence of water.[114] Denmark interpreted this as being due to competitive cleavage of the sulfonate by fluoride to give phenol in the absence of water. However, given that two equivalents of TMAF were employed and just 20% phenol was recovered after 24h suggests that this may not be the only factor; no control experiments using aryl halides in place of the nonaflates were reported.

1.4.2 Interactions of nucleophilic fluoride salts with organosilanes

Coordination of a nucleophile such as fluoride or hydroxide to the tetrahedral silicon centre of an organosilane cross-coupling partner results in re-hybridisation to a trigonal bipyramidal pentavalent species. The coordination is favoured if electron withdrawing substituents are already present on the silicon centre making it more electrophilic.[115] The polyhalosilanes, siloxanes and silanols that constitute the most effective substrates for cross-coupling are clearly predicated towards this type of interaction. The most electron withdrawing ligands generally prefer to occupy apical positions, interconversion between sites occurring by Berry pseudorotation.[116] Coordination of fluoride is particularly thermodynamically favourable because an extremely strong Si-F bond is formed.[117]

In anionic pentavalent complexes the negative charge is distributed over the axial nucleofuge centres α to the metal rather than being concentrated on the metal centre, thereby increasing the nucleophilicity of the ligands and the electrophilicity of the metal centre.[118-123] This results in enhanced polarisation of the key Si-C bond,[124] which, in the context of a catalytic cross-coupling cycle, would be expected to facilitate an associative transmetallation step.

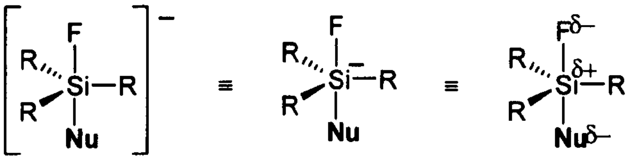


Figure 1.62: Coordination of a nucleophile increases the positive charge on the metal centre and the negative charge on the α ligands

The formation of a pentavalent complex enhances the rate of ligand exchange,[120] and it is likely that many of the polyheterosubstituted silanes that are competent in fluoride-promoted cross-coupling reactions (*e.g.* trifluoro-, trichloro- and trialkoxysilanes) react *via* common pentavalent intermediates containing fluoride and/or hydroxide ligands (*cf.* Denmark's silacyclobutanes and silanols).[96] The fact that qualitative differences exist between the coupling profiles of the various substrate types most likely simply reflects the relative rates of formation and eventual concentrations of the active species.

This explanation of activation should also be applicable to the examples of Stille couplings enhanced by nucleophiles (*cf.* Vedejs, Brown and Fu, *vide supra*).

Of course, if transmetallation occurs by an associative pathway there must be coordinative unsaturation at the group 14 metal centre that participates. Pentavalent species can react *via* hexavalent intermediates, but hexavalent group 14 organometallics will be unable to transmetallate without prior ligand dissociation. As indicated earlier in this discussion (section 1.3.1), this was the basis of Hiyama's proposal that trifluorosilanes were unreactive towards fluoride-promoted cross-coupling with alkenyl and aryl halides due to the formation of hexavalent pentafluorosilicates.[41,45,125]

It seems however, that more than hypervalency alone is needed to allow cross-coupling to take place, and that the precise nature of the hypervalent species may also have a crucial effect on transmetallation. This is consistent with observations that Heck reactions of alkenyltrialkylsilanes can be promoted by fluoride under conditions that do not allow cross-coupling.[126] Heck reactions proceed *via* a catalytic cycle that does not involve transmetallation, but pentavalent silane intermediates would still be expected to accelerate the key C-C bond forming step involving alkene insertion into the Si-C bond by virtue of the enhanced dipole across this bond. Denmark's discovery that silanols are particularly reactive towards cross-coupling in the presence of fluoride and water may hold the key to the additional requirements for efficient transmetallation.[96] In addition to facilitating the coordination of fluoride to silicon by forming a H-bonded fluoride adduct, the silanol may also allow coordination of the group 14 organometallic to the palladium centre. This process has been suggested as an alternative entry to boronic "ate" complexes that can render the transmetallation step in Suzuki cross-couplings intramolecular.[112,113,127]

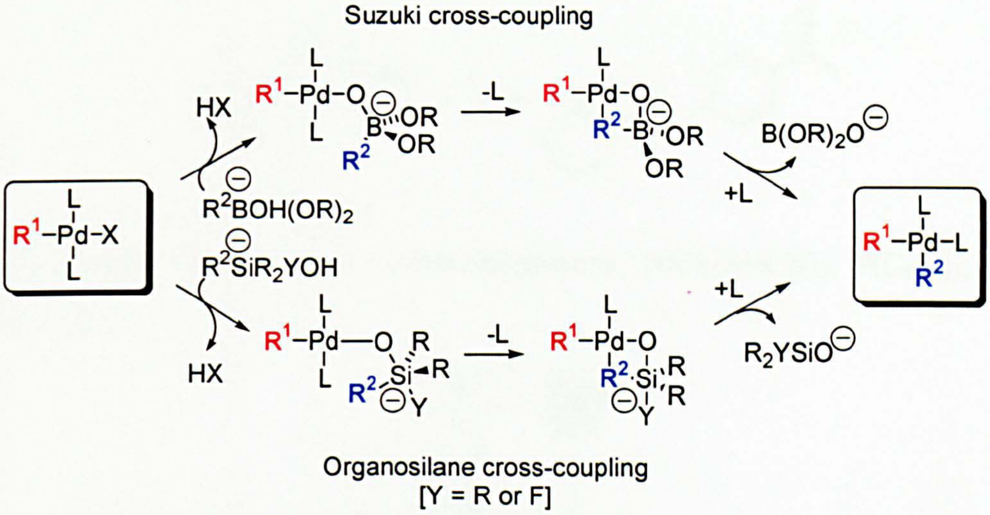
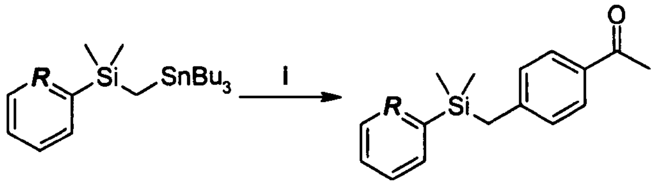


Figure 1.63: Proposed coordination of palladium by boronate or silicate

This proposed mechanism of intramolecular transmetallation for silicon is supported by the observation that basic, non-nucleophilic activators are also able to promote cross-coupling *via* deprotonation of the silanol to form a silanolate anion that activates a second silanol molecule intermolecularly.[85] Of course, it is also plausible that the involvement of dimers or higher aggregates may also play an important role in the fluoride mediated pathways, but there is no strong evidence for this so far.

Pre-coordination of the organometallic to palladium has also been proposed for the transfer of the (2-pyridyldimethylsilyl)methyl group from tin to palladium. The (trimethylsilyl)methyl group is known to be highly resistant to Stille coupling transfer and makes a better dummy ligand than even alkyl groups. Itami has reported that replacing a methyl group on silicon with a 2-pyridyl ring makes the system highly reactive to transfer.[103,128]



Reagents and conditions: i) 4-iodoacetophenone, $PdCl_2(MeCN)_2$, $P(C_6F_5)_3$, THF, 50°C, 24h.

R	Yield
N	84%
CH	-
N·HCl	-

Figure 1.64: Coordination driven silylmethyl transfer in Stille coupling

The importance of the pyridine nitrogen in coordination is underlined by the failure of the phenyl and protonated pyridyl analogues to undergo reaction. Furthermore, ^{119}Sn NMR analysis of the starting stannane revealed that there is no evidence for coordination of tin by nitrogen. Following reaction of the starting stannane with $PdCl_2(MeCN)_2$ ^1H NMR analysis of the pyridine protons revealed coordination of pyridine nitrogen to palladium.

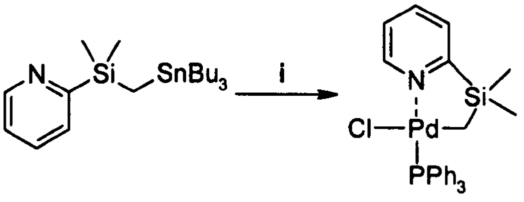


Figure 1.65: Coordination of 2-pyridyldimethylsilyl to palladium

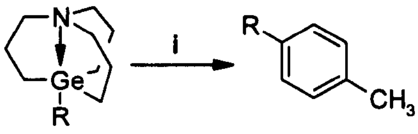
Reagents and conditions: i) $PdCl_2(MeCN)_2$, PPh_3, THF, 40°C, 69%.

Based on this evidence, it is proposed that the dramatic increase in reactivity of the pyridylsilyl group compared to the phenylsilyl group is due to the coordination of pyridine to palladium prior to transmetallation.

1.5 Organogermanium cross-coupling reactions

1.5.1 Carbagermatranes

Intramolecular coordination of a trans-annular nitrogen atom to a metal centre is known to activate group 14 metals (*vide supra*), and Kosugi has used a pentavalent carbagermatrane to successfully transfer alkynyl, alkenyl, allyl and aryl groups.[129]



Reagents and conditions: i) 4-bromotoluene, $Pd_2(dba)_3.CHCl_3$, P(*o*-Tol)$_3$, THF, sealed tube, 120°C, 24h.

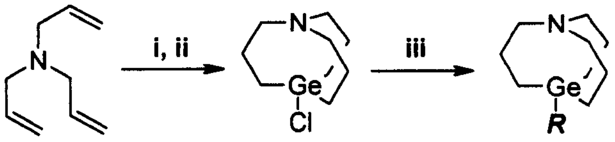
R Group	Yield
Butyl	8%
Allyl $^{(a)}$	88% (77%)$^{(b)}$
Phenyl	95% (85%)$^{(b)}$
Vinyl	82%
1-Ethoxyvinyl	59%
Phenylethynyl	67%

(a) PPh_3 used as ligand (b) Isolated yields in brackets

Figure 1.66: Kosugi's carbagermatrane cross-couplings

The trans-annular relationship between the amine and the metal allows for strong coordination of the germanium centre by the nitrogen lone pair, rendering it pentavalent, as evidenced by various spectroscopic and structural observations, including the lengthening of the Ge-C bond linking the group to be cross-coupled.[130] The pentavalent nature of the carbagermatrane is sufficient activation for these couplings to proceed in good yield *without* the addition of any intermolecular fluoride or base.

As coupling partners carbagermatranes are advantageous due to their stability towards a range of reaction conditions.[130] Like carbastannatranes, however, their utility is currently compromised by the lack of an efficient method for their synthesis. Kosugi adapted Vedejs' carbastannatrane synthesis involving hydrozirconation of triallylamine using Schwartz's reagent, transmetallation with germanium(IV) chloride (*cf.* tin(IV) chloride), and then reaction of the resulting 1-chloro-2,8,9-tricarbagermatrane with Grignard or organolithium reagents.[20,129]



Reagents and conditions: i) $Cp_2Zr(H)Cl$, $LiAlH_4$, THF, rt, 3h; ii) $GeCl_4$, -78°C → rt 4h, 89%; iii) ***R***-M (M = Mg or Li), THF, reflux.

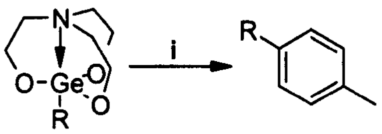
R Group	Yield
Butyl	74%
Allyl	82%
Phenyl	97%
Vinyl	98%
1-Ethoxyvinyl	86%
Phenylethynyl	11%

Figure 1.67: Synthesis of carbagermatranes

However, this route is heavily compromised by the high cost of Schwartz's reagent and difficulty of scale-up due to the high dilution conditions required.[131] Moreover, the reproducibility of this route has since been questioned in the literature,[132] and also by another researcher within our own group.[133] In 2000, a Merck process group published an evaluation of known routes to 1-chloro-2,8,9-tricarbastannatrane which culminated in the development of a disproportionation reaction between $N(CH_2CH_2CH_2SnBu_3)_3$ and $SnCl_4$ at 100°C followed by an acid/base extraction.[131,134] The potential of an analogous approach to 1-chloro-2,8,9-tricarbagermatrane preparation has not been assessed, but even if successful would be unattractive from the perspective of atom economy.

1.5.2 Germatranes

In order to overcome the drawbacks of using carbagermatranes in cross-coupling chemistry Faller investigated the use of germatranes, which can be synthesised from the corresponding trichlorogermanes and triethanolamine in the presence of base. This work was published in 2002 during the course of our own studies.[132]



Reagents and conditions: i) 4-iodotoluene, Pd(dba)$_2$, AsPh$_3$, TBAF, THF, 70°C.

R Group	Yield
Phenyl	43%
E-Styryl	64%
Z-Styryl (*E*/*Z* = 22/78)	73% (*E*/*Z* = 28/72)
Phenylethynyl[(a)]	91%

(a) P(t-Bu)$_2$(o-biphenyl) used as ligand in place of AsPh$_3$

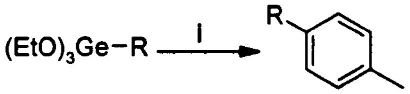
Figure 1.68: Faller's germatrane cross-couplings

Unlike Kosugi's carbagermatranes, the presence of fluoride is essential for germatranes to react, perhaps suggesting that the alkoxy substituents on germanium are not permanently bound to the metal centre. The cross-coupling yields are also poorer than those reported by Kosugi, and it seems that alkenylgermatranes may also participate in Heck reactions as all the *cis* alkenylgermatranes gave small or increased amounts of *trans* product in addition to the desired *cis* product.

In the context of their synthetic utility, germatranes are less attractive than carbagermatranes as they are unstable towards chromatography, and require trichloroorganogermanes as a starting material. In our hands, trichloroarylgermanes, although known, have been highly problematic to synthesise (*vide infra*).

1.5.3 Triethoxygermanes

Faller also carried out cross-couplings with phenyl- and phenylethynyl(triethoxy)germane as control experiments to determine the importance of coordination by the germatrane's trans-annular nitrogen in facilitating cross-coupling.[132]



Reagents and conditions: i) 4-iodotoluene, $Pd(dba)_2$, ligand, TBAF, THF, 70°C.

R Group	Ligand	Yield	Germatrane Yield
Phenyl	$AsPh_3$	25%	43%
Phenylethynyl	$P(t\text{-}Bu)_2$(*o*-biphenyl)	30%	91%

Figure 1.69: Faller's triethoxygermane cross-couplings

It can be seen that in both cases the internal coordination present in the germatrane offers significantly increased reactivity.

1.5.4 Trifurylarylgermanes

Oshima has developed trifurylgermane as a compound capable of carrying out a palladium catalysed germylation of aryl halides to give trifurylarylgermanes. Again, this work was published in the summer of 2002 during the course of our own studies.[135]

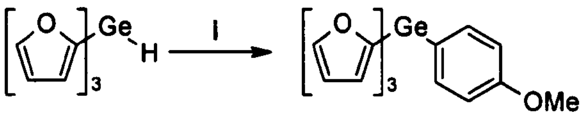
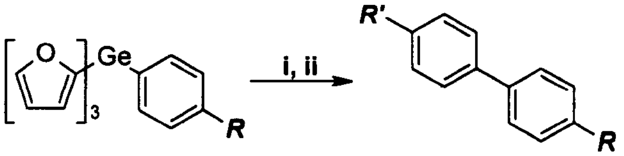


Figure 1.70: Oshima's trifurylarylgermane synthesis

Reagents and conditions: i) *p*-iodoanisole, $Pd(OAc)_2$, dppf, Cs_2CO_3, DMF, rt, 1.5h, 83%.

Trifurylarylgermanes are reactive coupling partners for a germyl cross-coupling reaction in the presence of fluoride, thus allowing a cross-coupling reaction using two aryl halides as the organic components.[135]



Reagents and conditions: i) TBAF (4eq, 1.0M in THF/H_2O), NMP, rt, 10min; ii) aryl halide, $Pd_2(dba)_3 \cdot CHCl_3$, P(2-furyl)$_3$, 100°C, 6.5h.

R	R'	Halide	Yield
p-Anisyl	Phenyl	Iodide	90%
p-Anisyl	Phenyl	Bromide	100%
p-Anisyl	*m*-Trifluoromethyl	Bromide	80%
p-Anisyl	1-Napthyl	Iodide	70%
p-Anisyl	*m*-Anisyl	Iodide	59%
m-Anisyl	Phenyl	Iodide	59%
m-Anisyl	*m*-Trifluoromethyl	Bromide	64%
m-Anisyl	1-Napthyl	Iodide	65%
Phenyl	*m*-Trifluoromethyl	Bromide	64%
Phenyl	1-Napthyl	Iodide	52%
E-Oct-1-enyl	Phenyl	Iodide	60%

Figure 1.71: Oshima's trifurylarylgermane cross-coupling

^1H and ^{19}F NMR analysis of the product from the reaction of trifurylarylgermanes with TBAF in THF/water revealed that there were no fluorines or furyl groups in the reactive organogermanium intermediate, allowing Oshima to tentatively suggest a trihydroxyarylgermane as the active cross-coupling species.

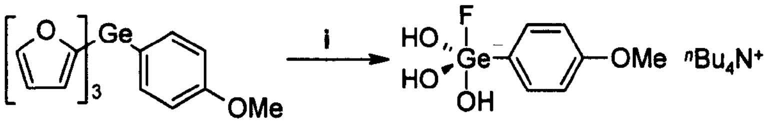


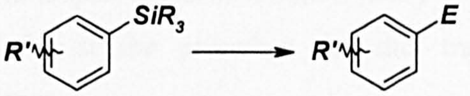
Figure 1.72: Proposed fluoride mediated cleavage of germanium-furyl bonds

Reagents and conditions: i) TBAF (4eq, 1.0M in THF/H_2O), THF, reflux, 5h.

2 Introduction to Friedel-Crafts demetallation

2.1 Cleavage of silicon-aryl bonds

The cleavage of Aryl-Metal bonds by electrophiles is a well known process for the Group 14 metals silicon, germanium and tin.[13] The range of practical electrophiles for cleaving aryl-silicon bonds includes:



Entry	Electrophile	Reference	Product
1	TFA	136	Ar-H
	$HClO_4$	13	
	H_2SO_4	13	
	CF_3SO_3H	137	
	HBF_4	138	
2	$Cl_2 + I_2/FeCl_3$	139	Ar-Cl
	$Cl_2/AcOH/H_2O$	140	
3	Br_2	136	Ar-Br
	$Br_2/AcOH/H_2O$	140	
4	ICl/dry AcOH	141	Ar-I
5	XeF_2	142	Ar-F
	$^{18}F_2/AcO^{18}F$	143	Ar-^{18}F
6	$H_2O_2/EtOH/KF$	144	Ar-OH
7	NO_2 or N_2O_4	145	Ar-NO_2
8	$Pb(OCOCF_3)_4$	146	Ar-OH
9	PCl_3	147	Ar-PCl_2
10	SO_3/CCl_4	148	Ar-SO_3SiMe_3
	SO_3/1,4-dioxane	149	
	$ClSO_3SiMe_3$	150	
11	RSO_2Cl/aluminium(III) chloride	151	Ar-SO_2R
12	i) BBr_3, ii) aq HCl	152	Ar-$B(OH)_2$
13	RCOCl/aluminium(III) chloride	153	Ar-COR
14	$PhCH_2Br$/aluminium(III) chloride	153	Ar-CH_2Ph
15	$ClSO_2NCO$	150	Ar-CN

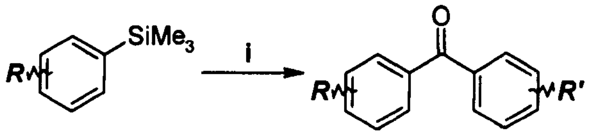
Table 2.1: Electrophilic cleavage of silicon-aryl bonds

The most relevant transformations to this project are those where cleavage and diversification of a library molecule can be accomplished with the simultaneous formation of a carbon-carbon bond (entries 13, 14 and 15).

Friedel-Crafts alkylation (entry 14) is generally low yielding, whilst cyanation using $ClSO_2NCO$ (entry 15) is unattractive due to the highly toxic nature of the reagents and the limited possibilities for further diversification. It was therefore decided to investigate the Friedel-Crafts *ipso*-acyldemetallation (entry 13) of arylgermanes. The following discussion looks at the precedent for this transformation involving arylsilanes and arylstannanes.

2.2 Acyldesilylation

The use of acyl chlorides in the presence of Lewis acid promoters to synthesise aryl ketones *via ipso* desilylation was first described in 1970 by Eaborn.[153]



Reagents and conditions: i) aromatic acyl chloride, aluminium(III) chloride, CS_2, 0°C, 30min, 46°C, 1.55h.

R	R'	Yield
p-Me	H	60%
o-OMe	H	73%
p-$SiMe_3$	*p*-$SiMe_3$	69%
p-Me	*m*-NO_2	76%
p-Cl	H	58%
o-Me	*o*-Me	68%

Figure 2.1. Acyldesilylation: Eaborn 1970

Since Eaborn published this first study, the chemistry has been widely used, but scarcely refined. A 1979 review by Effenberger collated work on acylative cleavage of carbon-silicon bonds up to that point and summarised the findings as follows:[154]

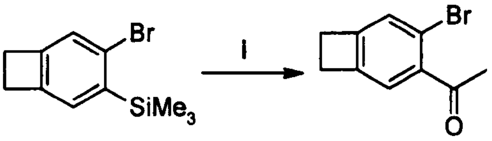
- Aryl C-Si bonds are 10^3-10^4 times more reactive towards AcCl + aluminium(III) chloride than aryl C-H bonds.

- Acetyl fluoride with BF_3 Lewis acid does not react exclusively at the *ipso* position.

- Strong electron donating substituents (*e.g.* NMe_2: $\sigma^+ = -1.7$, NH_2: $\sigma^+ = -1.3$, OH: $\sigma^+ = -0.92$, OMe: $\sigma^+ = -0.78$) will direct the substitution regardless of the position of the $SiMe_3$ group.

Some of the applications of this chemistry are shown below:

Vollhardt cyclised bis(trimethylsilyl)acetylene with various α,ω-diynes in the presence of $CpCo(CO)_2$ to synthesise 4,5-bis(trimethylsilyl)benzocyclobutanes, indanes and tetralins, and further explored the electrophilic substitution of these compounds. Following a selective mono bromodesilylation, he was able to achieve an acetyldesilylation using Eaborn's conditions.[155]

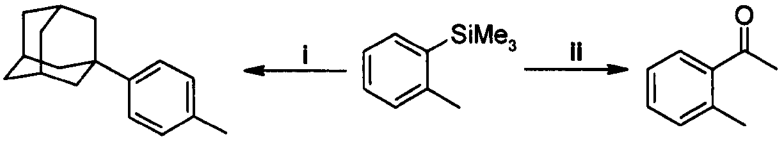


Reagents and conditions: i) AcCl, aluminium(III) chloride, CS_2, rt, 5h, 56%.

Figure 2.2: Vollhardt's 1977 acetyldesilylation of benzocyclobutanes

The cyclisation to form tetralins was later adapted as the cornerstone of an elegant steroid synthesis, involving a selective bromodesilylation.[146]

The importance of steric effects in Friedel-Crafts alkylations and acylations was underscored by the work of Sasaki.



Reagents and conditions: i) 1-adamantyl chloride, aluminium(III) chloride, CH_2Cl_2, -78°C, 80%; ii) AcCl, $TiCl_4$, CH_2Cl_2, -78°C, 45%.

Figure 2.3: Sasaki's 1980 $TiCl_4$ promoted acetyldesilylation

Sasaki was attempting to alkylate *o*-tolyltrimethylsilane using adamantyl chloride, however only the *para* isomer was isolated. The *para* isomer was also obtained in 75% yield when *m*-tolyltrimethylsilane was employed. However, *acetyl*ation of the same compound gave the desired *ortho* isomer, albeit in low yield. This reaction is noteworthy for the use of CH_2Cl_2 as solvent in place of carbon disulfide as used by Eaborn (*vide supra*).[156]

Work by Dunogue further illustrates some interesting facets of this chemistry:

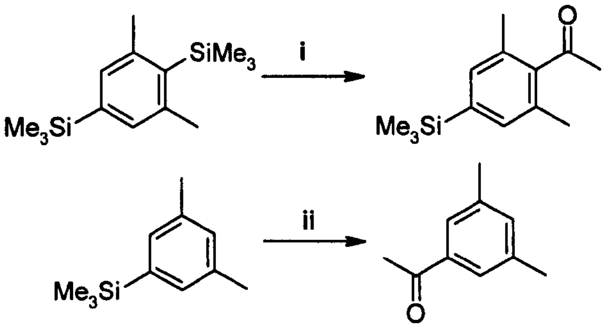
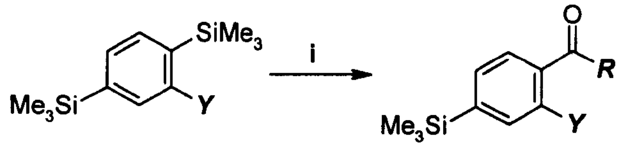


Figure 2.4: Dunogues' 1980 functionalisation of xylenes

Reagents and conditions: i) AcCl, aluminium(III) chloride, CH_2Cl_2, 0°C 30min, -40°C 2h, 91%; ii) conditions as for i), 88% yield.

Di-TMS substituted aryls will only undergo one cleavage due to the deactivating effect of the newly installed carbonyl group. Where there is a choice of two TMS groups the directing effect of other substituents, or steric considerations become important, whilst if there is no choice then *ipso* substitution takes precedent of the effects of weak or moderate directing groups.[157]



Reagents and conditions: i) RCOCl, aluminium(III) chloride, CH_2Cl_2.

Y	R	Temperature	Time	Yield
F	AcCl	-80°C → 40°C	3h	79%
F	PhCOCl	Rt → 44°C	18h	52%
Et	AcCl	-80°C → 40°C	3h	68%
Et	PhCOCl	Rt → 44°C	12h	41%

Figure 2.5: Dunogues' 1990 functionalisation of fluoro and ethylbenzenes[158]

In 1981 Fleming exemplified the use of his dimethylphenylsilyl group, by synthesising vinyl dimethylphenylsilanes from the reaction of bis(dimethylphenylsilyl)cuprate with acetylenes. In order to demonstrate that the dimethylphenylsilyl group does not interfere with vinylsilane chemistry he selectively cleaved the vinylsilane bond with AcCl/aluminium(III) chloride.[159] No acetophenone was observed.

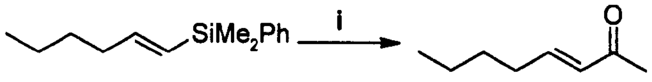


Figure 2.6: Fleming's 1981 cleavage of vinylsilanes

Reagents and conditions: i) AcCl, aluminium(III) chloride, CH_2Cl_2, 0°C, 30min, 69%.

Silylated acenaphthylenes can also be acyldemetallated.[157]

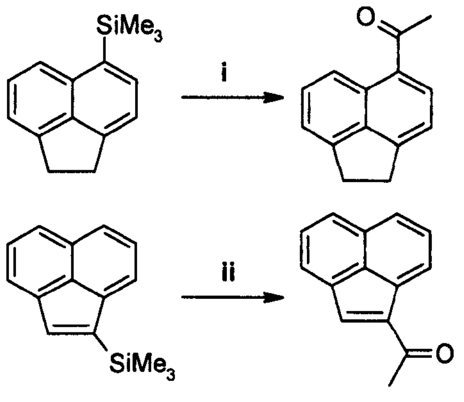


Figure 2.7: Dunogues' 1982 acetylation of silyl substituted acenaphthylenes

Reagents and conditions: i) AcCl, aluminium(III) chloride, CH_2Cl_2, 0°C 30min, -40°C 2h, 80%; ii) conditions as for i), 35% yield.

As part of his studies towards the synthesis of ergot alkaloids produced by the fungus *Claviceps*, Barrett investigated the acyldesilylation of 4-(trimethylsilyl)indole.[160]

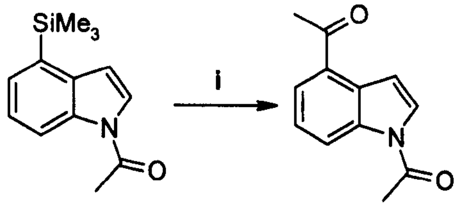


Figure 2.8: Barrett's 1984 acetylation of silyl substituted indoles

Reagents and conditions: i) AcCl, aluminium(III) chloride, CH_2Cl_2, 17h, rt, 95%.

In order to obtain the observed selectivity for *ipso*-desilylative acylation at the C-4 position it was necessary to first deactivate the C-3 position by forming the *N*-acyl compound.

Katz has utilised the *ipso* directing effect of trimethylsilyl groups in his work towards the synthesis of chiral helicenes.[161-163]

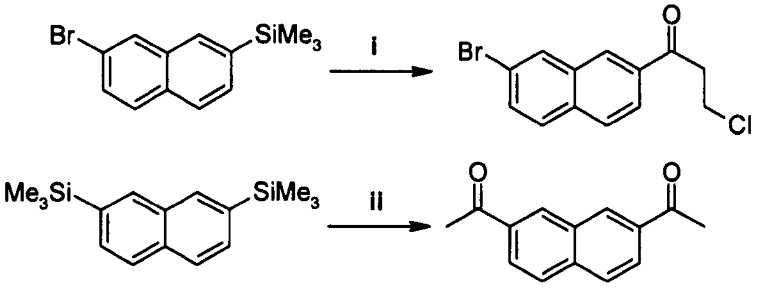


Figure 2.9: Katz acylation of silyl substituted naphthalenes (1986, 1993, and 1997)[161-163]

Reagents and conditions: i) $ClCH_2CH_2COCl$, aluminium(III) chloride, CH_2Cl_2, -78°C, 1.5h, 76%; ii) Ac_2O, aluminium(III) chloride, CH_2Cl_2, 0°C, 40min, 86%.

The use of the TMS group allows the naphthalene ring to be acylated selectively at the 7-position, rather than the 6 or 8 positions.

Shudo investigated the synthesis of aromatics with trimethylsilyl or trimethylgermyl groups in place of a *tert*-butyl group in a compound of known anti-leukaemic activity.[164]

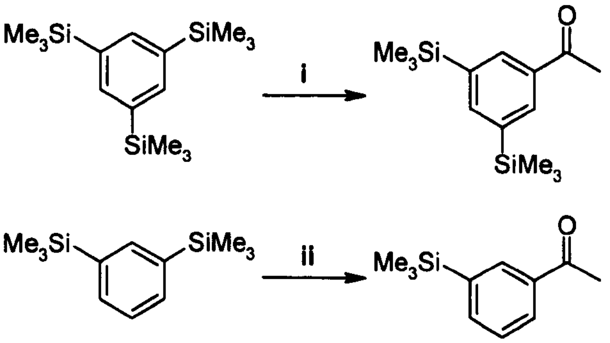


Figure 2.10: Shudo's 1990 acylation of tri-silylbenzene

Reagents and conditions: i) AcCl, aluminium(III) chloride, CS_2, 0°C, 77%; ii) conditions as for i), 7% yield.

Acyldesilylation of 2,4,6-tris(trimethylsilyl)benzene or 1,3-bis(trimethylsilyl)benzene gave the corresponding acetophenones, which were further transformed to chalcones.

2.3 Acyldegermylation

Maire has reported that phenyltrimethylgermane, phenyltrimethylsilane and phenyltrimethylstannane, can be acetyldemetallated by the action of AcCl/aluminium(III) chloride. However, there is no specific detail given for acyldegermylation in the paper.[165]

2.4 Acyldestannylation

The earliest mention of acyldestannylation was in Eaborn's seminal work of 1970, extending the reaction from silicon to tin. No reaction occurred in the absence of aluminium(III) chloride.

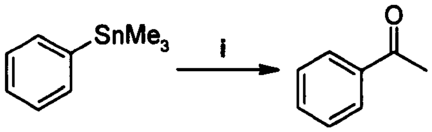
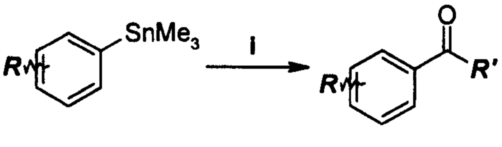


Figure 2.11: Eaborn's acyldestannylation[153]

Reagents and conditions: i) AcCl, aluminium(III) chloride, CS_2, -30°C, 30min, 98%.

Neumann further exemplified this chemistry in 1989.



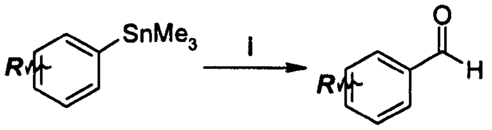
Reagents and conditions: i) R'COCl, aluminium(III) chloride, CH_2Cl_2, -30°C, 2h.

R	R'	Yield	Isomers
p-Tolyl	Methyl	60%	-
m-Tolyl	Methyl	83%	*m*/*p* 97/3
m-Tolyl	Phenyl	50%	*m*/*p* 65/35
m-Tolyl	t-Butyl	100%	(a)
p-Chloro	Methyl	60%	-
p-Chloro	Phenyl	40%	-

(a) 77/23 mixture of ketone (meta/para 94/6) / t-butyl toluene (meta/para 85/15)

Figure 2.12: Neumann's tin mediated Friedel-Crafts acyldestannylation[166]

In addition to highly activated anilines and phenols, arylstannanes are also reactive towards *ipso*-formyldestannylation.



Reagents and conditions: i) *N*-Methyl-*N*-phenylformamide, $POCl_3$, 70°C, 3h.

R	Yield
H	56%
p-Tolyl	70%
m-Tolyl	55%
p-Anisyl	96%
o-Anisyl	79%
p-Chloro	10%

Figure 2.13: Neumann's tin mediated Vilsmeier formylation[166]

Acyldemetallation of both arylsilanes and arylstannanes is accomplished using identical reagents, but varying the reaction time and temperature. As the reactivity of group 14 aryl-metals with electrophiles is largely a function of the β-effect[167,168] this precedent for silicon and tin should also be applicable to acyldegermylation.

3 Organogermanium linker cleavage with carbon electrophiles

3.1 Background to the project

Like organotin[169,170] and organosilicon[171,172] compounds, organogermanium species have previously been shown to be useful as linkers in solid phase chemistry.[173] Like other group 14 metal based linker constructs they are most applicable to the solid phase synthesis of molecules with an aromatic core.

Ellman was the first to use a germanium analogue of an organosilicon linker to demonstrate the synthetic utility of germanium linker molecules in the combinatorial solid phase synthesis of benzodiazepines.[174]

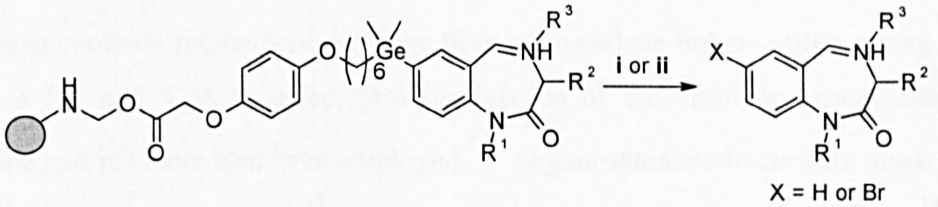


Figure 3.1: Ellman's germanium based linker for combinatorial synthesis of benzodiazepines

Reagents and conditions: i) TFA; ii) Br_2.

In this case, the use of germanium in place of silicon allowed cleavage of the electron deficient benzodiazepines with electrophiles milder than HF.

Of more interest to this study is Spivey's germanium linker molecule that has been previously developed in these laboratories and has been shown to be applicable to the combinatorial synthesis of pyrazoles,[175,176] pyrimidines,[177] and oligothiophenes.[178]

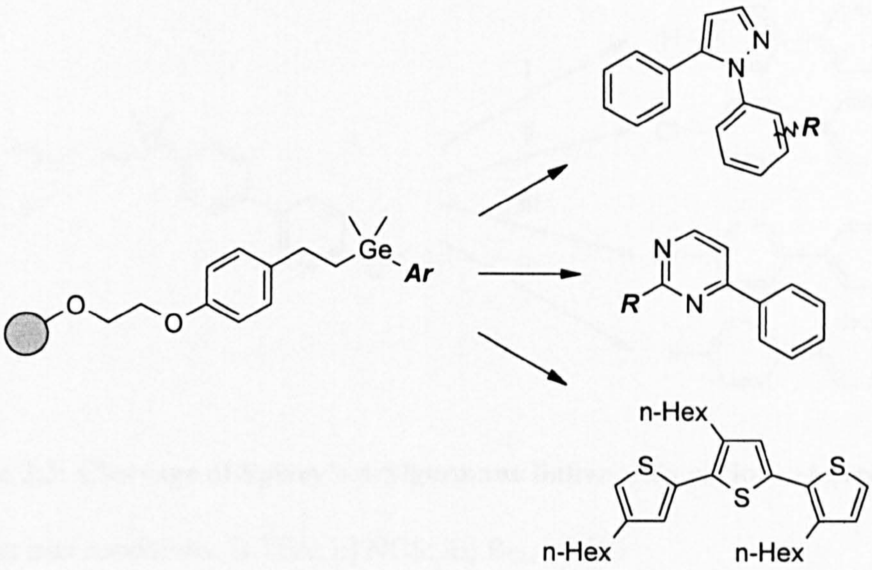


Figure 3.2 Spivey's germanium based linker

The most common methods of cleavage from organosilane linkers utilise strong acids such as HF and TFA to effect protodesilylation of the aromatic group, although bromine and ICl have also been employed.[174] Organostannane linkers are much more reactive towards electrophiles[13] and have also been cleaved by bromine,[166] ICl,[179] and NaI in the presence of an oxidant,[180] Spivey has shown that germanium linkers are also sufficiently reactive towards electrophiles to be cleaved by halonium ions including NCS to give analytically pure haloaromatics.[175,176]

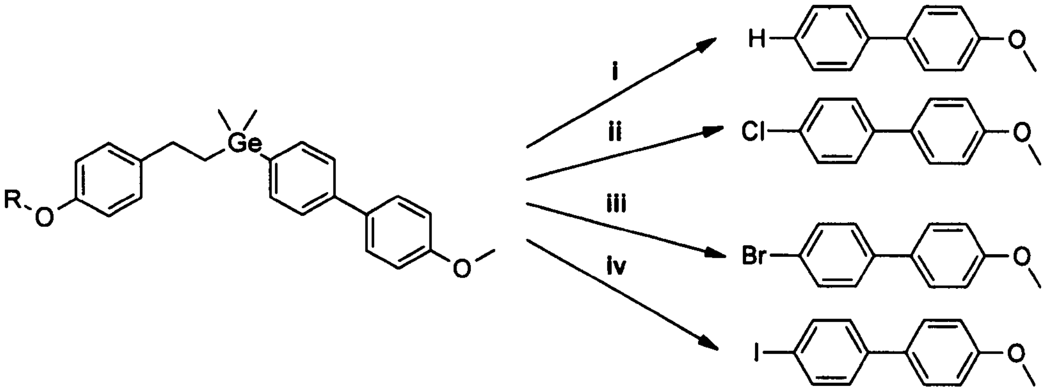


Figure 3.3: Cleavage of Spivey's arylgermane linker with various electrophiles

Reagents and conditions: i) TFA; ii) NCS; iii) Br_2; iv) ICl

3.2 Aims and objectives of the project: Cross-coupling

A useful extension to the cleavage protocols already employed would be the ability to use carbon based electrophiles in the cleavage. This would offer another opportunity to incorporate functionality into the molecule during the otherwise diversity redundant cleavage step. One of the more obvious potential approaches, in the light of precedent with tin and silicon, is the development of an arylgermane cross-coupling protocol, *i.e.* a "Germyl-Stille" or "Germyl-Hiyama" reaction. A palladium catalysed reaction between arylgermanes and easily varied aryl halides would offer an inherent increase in the diversity of the substrate during the cleavage step. The resulting biaryl motif is commonly seen in pharmaceuticals and agrochemicals.

Limited success had already been obtained from undergraduate studies. The work described in the following chapters has built on these preliminary studies.[181]

The primary objective of the research was to develop, optimise and delineate the scope of this type of reaction in the context of a linker cleavage protocol. In order to achieve this objective, there were three aims for the project:

1. To synthesise a relevant solution phase model system on which to test experimental conditions.

2. To identify a suitable method to appropriately activate arylgermanes, most likely *via* the formation of pentavalent germanate complexes.

3. To develop a compatible catalyst system. It was anticipated that some of the compromises required of the catalyst during the reaction cycle would need to be overcome in order to facilitate the crucial transmetallation step.

3.3 Aims of the project: Friedel-Crafts degermylation

A complementary protocol to cross-coupling cleavage, which would also benefit from concomitant carbon-carbon bond formation, would be Friedel Crafts *ipso*-acyldegermylation, as discussed for silicon and tin in chapter 2.

The primary objective of the research in this area was to identify suitable reaction conditions based on the existing work with silicon and tin. These conditions would then be applied to a variety of arylgermanes in order to determine the scope of *ipso*-degermylation using acylium ions.

The progress made towards these two synthetic challenges is described in the following two chapters.

4 Cross-coupling results and discussion

4.1 Approaches towards dimethylarylgermane cross-coupling

4.1.1 Activation of group 14 organometallics.

As described in chapter 1, cross-coupling reactions of group 14 organometallics are widely known with tin, but are also becoming increasingly prevalent with silicon. Organostannanes are usually sufficiently reactive to transmetallate with palladium without further activation; even in unfavourable cases the addition of an intermolecular nucleophile is usually enough to facilitate coupling. Silicon is markedly less reactive and usually requires pre-activation of the silicon centre itself as well as the addition of an intermolecular nucleophile.

At the time this project commenced, the only known example of an organogermane cross-coupling was that of Kosugi's carbagermatrane, which suggested that a hypervalent organogermane would indeed couple successfully. In light of this, it was hypothesised that even in the *absence* of fluoride, the reactivity of germanium was probably intermediate between silicon and tin. Furthermore, owing to the fact that germanium is known to be more susceptible towards hypervalency than silicon,[118] it was believed that the reactivity of an organogermane would be closer to tin than to silicon. Consequently, it was anticipated that only an intermolecular nucleophile may be required to secure activation, and that pre-activation of the germanium centre would not be needed.

4.1.2 Starting point

Previous work and experience from undergraduate studies,[181] coupled with an understanding of the mechanism of cross-coupling, enabled a tentative starting point to be identified. The solution-phase model tolylgermane **1** was chosen as a suitable compound for initial studies. This compound contains an electron neutral aryl group, with a benzylic methyl group that could act as a convenient NMR marker. Bromobenzonitrile **2** was selected as the initial coupling partner as it is an electron-deficient aryl bromide that should be highly reactive towards oxidative addition. The presence of the bromide was also expected to provide a good compromise in terms of the reactivity of the aryl halide towards oxidative addition, and of the arylpalladium(II) halide towards transmetallation. Commercial $Pd_2(dba)_3$ was used as the palladium source, and triphenylphosphine was employed as the initial phosphine as these catalyst components are commonly used in cross-coupling chemistry. Dimethylformamide was used as the solvent as this had been shown to give the highest consumption of arylgermane in fourth year experiments.[181]

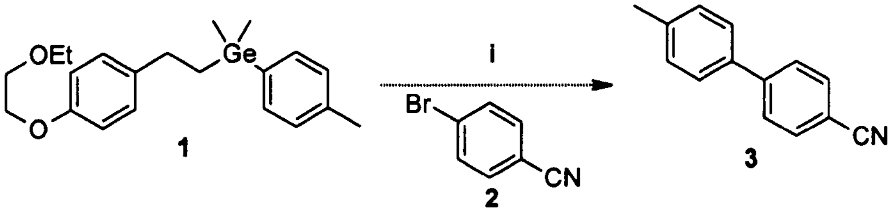


Figure 4.1: Proposed starting point for cross-coupling reaction studies

Reagents and conditions: i) $Pd_2(dba)_3$, PPh_3, *fluoride*, DMF

The first step was to look at various fluoride sources in order to determine the optimal activation of the organogermane. Once this had been achieved it was intended to delineate the scope of the reaction *via* a combinatorial scanning experiment looking at the effect of varying the aryl group on germanium and the aryl halides. Finally, the catalyst and reaction conditions would be optimised by screening various phosphines and solvents.

For the scanning experiment it was planned to use tolyl, anisyl and acetophenyl groups, as electron neutral, electron rich and electron deficient aryl groups respectively, on germanium. Bromo- and iodobenzonitriles were chosen as electron deficient aryl halides, bromo- and iodobenzene as the electron neutral aryl halides and bromo *N,N*-dimethylaniline as the electron rich halide.

In order to analyse the large number of reaction mixtures that this approach would involve, it was decided to initially analyse each experiment using quantitative GC/MS to gain an estimate of the yield before isolating the product from the most promising experiments. Such an approach also required the synthesis of authentic products and calculation of response factors relative to an internal standard.

4.1.3 Synthesis of reaction materials

A rapid and efficient synthesis of dimethylarylgermane linkers and solution phase models starting from germanium(IV) chloride had been previously developed in the group.[175] Germanium(IV) chloride **6** is initially reduced to give a germylidene species **7**, which is then inserted into the homobenzyl activated C-Cl bond of chlorophenol **5**, and the resulting trichlorogermylphenol **8** exhaustively methylated.

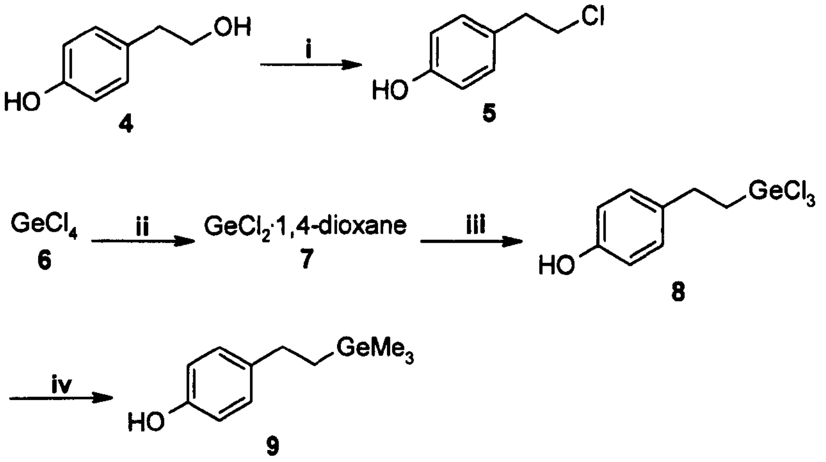


Figure 4.2: Synthesis of trimethylgermylphenol

Reagents and Conditions: i) c.HCl, 100°C, 3h (90%); ii) TMDS, 1,4-dioxane 110°C 3h (75%); iii) **5**, 140°C, 17h (74%); iv) MeMgBr, toluene, 110°C, 16h, (73%).

The resulting trimethylgermylphenol **9** was then protected as an ethoxyethyl ether to give trimethylgermane **10**, and selectively chlorodemethylated to give the activated chlorodimethylgermane **11**.

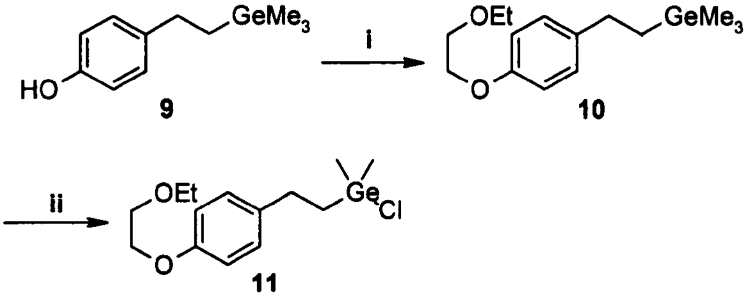


Figure 4.3: Synthesis of aryldimethylgermane solution phase model

Reagents and Conditions: i) Cs_2CO_3, TBAI, MeCN, 2-chloroethyl ethyl ether (92%); ii) $SnCl_4$, $MeNO_2$, 50°C, 17h (100%).

The desired tolylgermane **1** was synthesised by the reaction of chlorodimethylgermane **11** and commercial *p*-tolyl magnesium bromide in 76% yield.

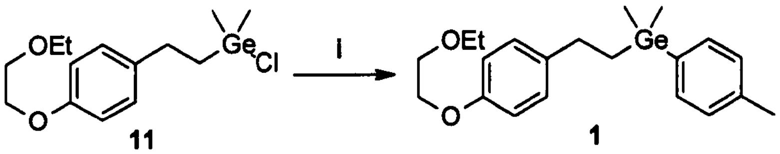


Figure 4.4: Synthesis of dimethyltolylgermane

Reagents and Conditions: i) *p*-TolMgBr, THF (76%).

For the scanning experiment an electron rich and electron deficient arylgermane were also needed; anisylgermane **13** was synthesised from chlorodimethylgermane **11** and anisole **12**.

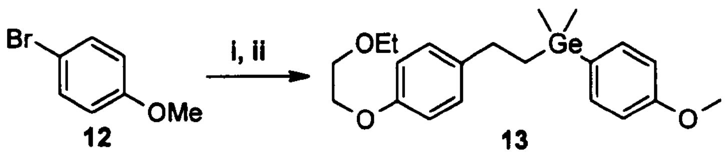


Figure 4.5: Synthesis of dimethylanisylgermane

Reagents and Conditions: i) n-BuLi, THF, -78°C, 1h, ii) **9**, THF, -78°C → rt 2h (43% i-ii).

Synthesis of acetophenylgermane **16** required the formation of the diethylacetal of 4-bromoacetophenone **14**, which was quickly and cleanly accomplished using catalytic NBS in EtOH.[182] The resulting aromatic acetal **15** was lithiated and quenched with chlorodimethylgermane **11**. Deprotection of the crude acetal was accomplished using PPTS.[175]

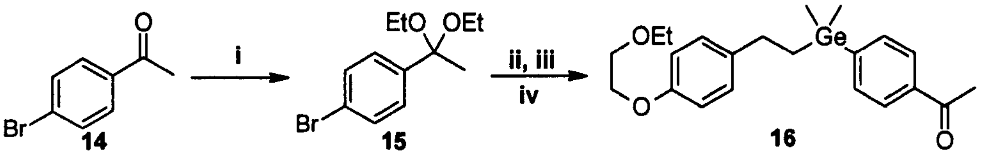


Figure 4.6: Synthesis of dimethylacetophenylgermane

Reagents and Conditions: i) NBS, $HC(OEt)_3$, EtOH, 17h (93%); ii) n-BuLi, THF, -78°C, 1h, iii) **11**, THF, -78°C, 17h; iv) PPTS, acetone, H_2O, 56°C, 17h (86% ii-iv).

Of the aryl halides being used in the scanning experiment, only 4-iodobenzonitrile **18** was not commercially available, and this was synthesised *via* diazotisation of 4-aminobenzonitrile **17** followed by reaction with NaI.[183]

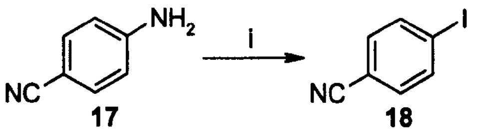
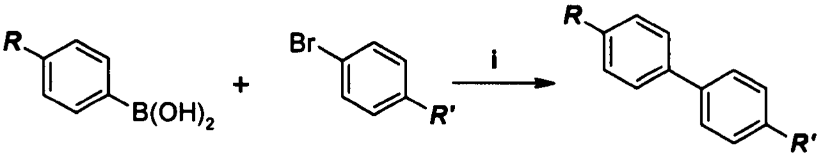


Figure 4.7: Synthesis of 4-iodobenzonitrile

Reagents and Conditions: i) $NaNO_2$, H_2SO_4, H_2O, -5°C, 30min; ii) NaI, -5°C → rt, (64%).

4.1.4 "Authentic" product synthesis

In order to monitor the cross-coupling reactions and assess their yields by quantitative GC/MS it was necessary to calculate response factors for the authentic products. Of the 9 possible products 3 were commercially available; 4-methylbiphenyl **19**, 4-methoxybiphenyl **20**, and 4-acetylbiphenyl **21**, and one was eventually not needed; 4-acetyl-4'-dimethylaminobiphenyl. The remaining six compounds were synthesised *via* Suzuki reactions in a reaction carousel using the appropriate arylboronic acids and aryl halides.



Reagents and Conditions: i) Pd(PPh_3)$_4$, NaOH (aqueous), EtOH, toluene, 90°C, 17h.

R	R'	Product	Yield
Me (**22**)	NMe_2 (**25**)	**26**	22%
OMe (**23**)	NMe_2 (**25**)	**27**	16%
OMe (**23**)	CN (**2**)	**28**	38%
Ac (**24**)	CN (**2**)	**29**	64%

Figure 4.8: "Authentic" product synthesis

The final authentic product for analytical purposes, 4-cyano-4'-methyl-biphenyl **3**, was synthesised by a one-pot Negishi reaction according to a literature procedure for the synthesis of an intermediate to potential inhibitors of P450 enzymes.[184]

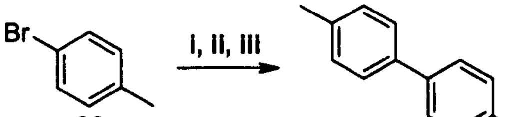


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Figure 4.9 Synthesis of 4-cyano-4'-methyl-biphenyl

Reagents and Conditions: i) t-BuLi, THF, -78°C; ii) $ZnCl_2$, THF, -78°C → rt, 1.5h; iii) benzonitrile **2**, Pd(PPh_3)$_4$, THF, 70°C, 2.5h (35%).

The literature procedure for purification of biaryl **3**, following an aqueous extraction, was recrystallisation from isopropanol. Analysis of the recrystallised product by ^{1}H NMR revealed that in fact the sample was a co-crystallised (*ca.* 1:1) mixture of the desired product and 4,4'-dimethylbiphenyl. The impurity results from the homo-coupling of 4-methylphenylzinc chloride. The procedure was modified to include column chromatography, which allowed the authentic product **3** to be obtained as analytically pure white needles.

With the authentic products in hand, it was then possible to calculate the response factors relative to an internal standard. Naphthalene was chosen as the standard as it eluted well away from any other peaks in the GC/MS chromatogram. Solutions were made up containing a known amount of naphthalene with a known equimolar amount of the authentic product and then analysed three times before taking an average value of the ratio of naphthalene molar peak area to the authentic product molar peak area.

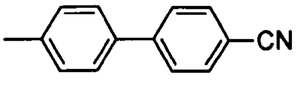
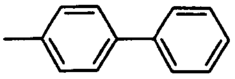
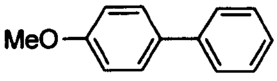
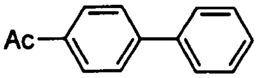
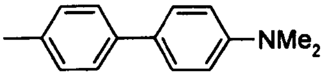
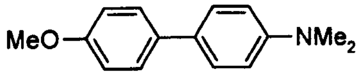
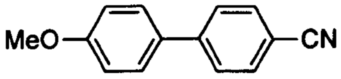
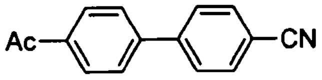
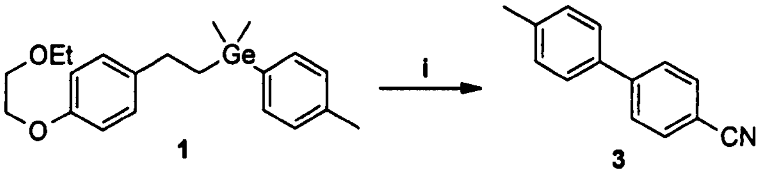
Authentic product		**Response factor relative to naphthalene**
	**3**	0.341 (± 0.003)
	**19**	0.913 (± 0.007)
	**20**	0.833 (± 0.006)
	**21**	0.508 (± 0.004)
	**26**	0.513 (± 0.004)
	**27**	0.788 (± 0.006)
	**28**	0.683 (± 0.006)
	**29**	0.558 (± 0.004)

Table 4.1: Product response factors relative to naphthalene internal standard for "authentic" product biaryls

4.1.5 Scanning experiment: Initial fluoride experiments

Precedent with silicon (*vide supra*) has demonstrated the fundamental importance of the activator in Group 14 organometallic cross-coupling reactions. The first cross-coupling reactions therefore were directed towards looking at the effect of fluorides on cross-coupling in order to hopefully identify a robust initial reaction to use as a base for further fine-tuning and optimisation.

Tolylgermane **1** was reacted with benzonitrile **2** in DMF, using a $Pd_2(dba)_3/PPh_3$ catalyst system and various fluorides, heated in a sealed reaction vial. The fluorides were weighed out under a stream of anhydrous nitrogen gas to keep deliquescence to a minimum.



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Reagents and Conditions: i) 4-bromobenzonitrile, $Pd_2(dba)_3$ (5mol% Pd), PPh_3 (10mol%), fluoride (2.2eq), DMF, 48h.

Fluoride	Temperature	GC/MS yield	Isolated Yield
TBAF·3H_2O	130°C	0.1%	-
KF	130°C	13%	-
BnTMAF	130°C	32%	22%
KF and 18-crown-6	130°C	8%	-
KF and 18-crown-6	150°C	15%	-

Figure 4.10: Cross-coupling experiments with fluoride variable

CsF was also investigated separately with BnTMAF as a control experiment.

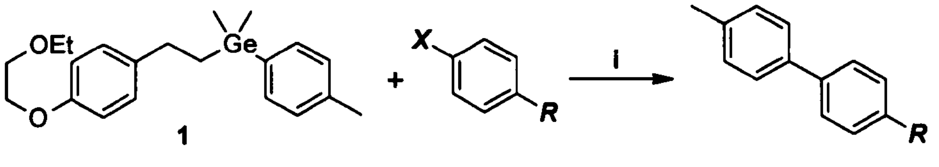
Fluoride	Temperature	GC/MS yield
BnTMAF	130°C	1.4%
CsF	130°C	7%

Table 4.2:Comparison of BnTMAF and CsF as cross-coupling activator

These experiments appeared to confirm the contention that the activator is critically important with yields varying from the trace level, to an isolated 22%. BnTMAF initially appeared to be the best activator, but in a further investigation CsF seemed to be superior to BnTMAF. However, the reproducibility of these reactions was *very* poor; the BnTMAF-promoted yield of 22% obtained in the initial experiments was never reproduced. In spite of this, it was decided to proceed with both BnTMAF and CsF as activators for the combinatorial scanning experiment.

4.1.6 Scanning experiment

The cross-coupling of dimethylarylgermanes with 4-bromo- (**2**) and 4-iodobenzonitrile (**18**), bromo- (**31**) and iodobenzene (**32**), and 4-bromo-*N,N*-dimethylaniline (**25**), in the presence of CsF and BnTMAF was investigated using a combinatorial approach. The results are presented in figure 4.11 for tolylgermane **1**, in figure 4.12 for anisylgermane **13**, and in figure 4.13 for acetophenylgermane **16**.

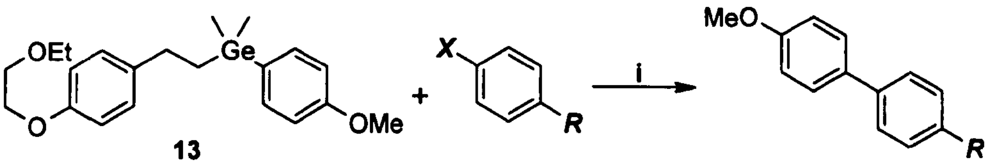


Reagents and Conditions: i) $Pd_2(dba)_3$ (5mol% Pd), PPh_3 (10mol%), fluoride (2.2eq), DMF, 150°C, 48h.

R	*X*	Aryl halide	Fluoride	Product	GC/MS yield
CN	Br	**2**	BnTMAF	**3**	1%
CN	Br	**2**	CsF	**3**	33%
CN	I	**18**	BnTMAF	**3**	Not observed
CN	I	**18**	CsF	**3**	4%
H	Br	**31**	BnTMAF	**19**	31%
H	Br	**31**	CsF	**19**	6%
H	I	**32**	BnTMAF	**19**	Not observed
H	I	**32**	CsF	**19**	8%
NMe_2	Br	**25**	BnTMAF	**26**	8%
NMe_2	Br	**25**	CsF	**26**	Not observed

Figure 4.11: Scanning experiment: tolylgermane cross-couplings

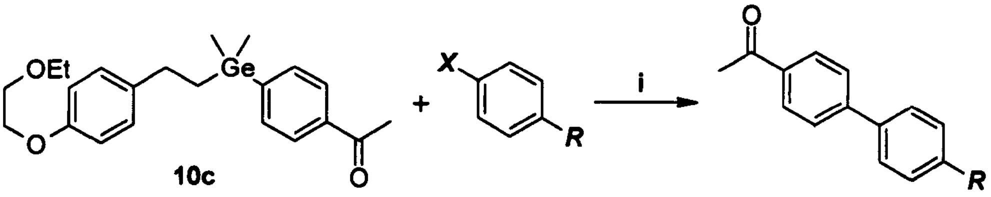
The high degree of variability was a concern and led to a change in the sampling method. Previously the reactions had been worked up to give a crude sample, to which a known amount of naphthalene was added before analysing the mixture. In order to both speed up analysis and decrease the potential for error, the reaction mixtures were sampled directly. A known volume of reaction solution was removed, a known volume of naphthalene standard solution added, and the mixture then diluted and analysed by GC/MS.



Reagents and Conditions: i) $Pd_2(dba)_3$ (5mol% Pd), PPh_3 (10mol%), fluoride (2.2eq), DMF, 150°C, 48h.

R	*X*	Aryl halide	Fluoride	Product	GC/MS yield
CN	Br	**2**	CsF	**28**	28%
CN	Br	**2**	BnTMAF	**28**	0.7%
CN	I	**18**	CsF	**28**	2.5%
CN	I	**18**	BnTMAF	**28**	Not observed
H	Br	**31**	CsF	**20**	1.3%
H	Br	**31**	BnTMAF	**20**	19%
H	I	**32**	CsF	**20**	4%
H	I	**32**	BnTMAF	**20**	1.3%
NMe_2	Br	**25**	CsF	**27**	Not observed
NMe_2	Br	**25**	BnTMAF	**27**	16%

Figure 4.12: Scanning experiment: anisylgermane cross-couplings



Reagents and Conditions: i) $Pd_2(dba)_3$ (5mol% Pd), PPh_3 (10mol%), fluoride (2.2eq), DMF, 150°C, 48h.

R	*X*	Aryl halide	Fluoride	Product	GC/MS yield
CN	Br	**2**	BnTMAF	**29**	3%
CN	Br	**2**	CsF	**29**	15%
CN	I	**18**	BnTMAF	**29**	Not observed
CN	I	**18**	CsF	**29**	13%
H	Br	**31**	BnTMAF	**21**	7%
H	Br	**31**	CsF	**21**	1.0%
H	I	**32**	BnTMAF	**21**	2.5%
H	I	**32**	CsF	**21**	11%
NMe_2	Br	**25**	BnTMAF	**33**	Not observed
NMe_2	Br	**25**	CsF	**33**	Not observed

Figure 4.13: Scanning experiment: acetophenylgermane cross-couplings

On initial inspection, the results from figures 4.11, 4.12 and 4.13 appear to present few, if any, clear trends. However, following careful analysis they do allow some trends to be identified and conclusions drawn. Of the three dimethylarylgermanes used (**1**, **13**, and **16**), acetophenylgermane **16** performed consistently worse than both tolylgermane **1** and anisylgermane **13**. Of these two compounds, tolylgermane **1** gave higher coupling yields. This is broadly consistent with literature precedent for arylsilane cross-coupling reactions, in which electron rich nucleophiles are more smoothly transferred than electron deficient systems. Bromides appear to be better coupling partners than the corresponding iodides, again in agreement with existing precedent. Another predictable conclusion is the superiority of the electron deficient benzonitrile coupling partner when compared to the electron neutral phenyl group. The electron rich dimethyl aniline was generally unreactive. The following reagent combination appeared to be optimal (figure 4.14).

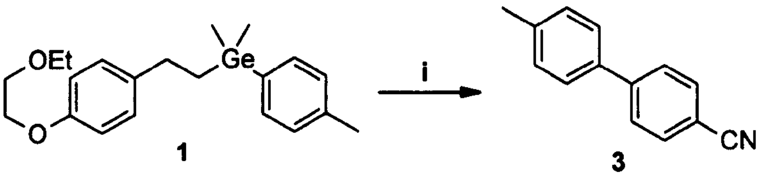


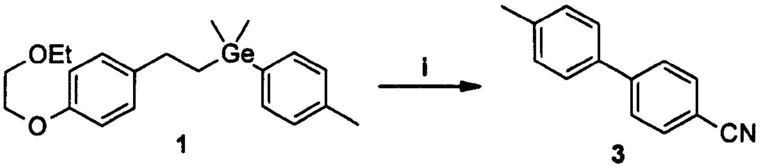
Figure 4.14: Best case coupling identified by scanning experiment

Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (5mol% Pd), PPh_3 (10mol%), DMF, 150°C, 48h, GC/MS yield 33%.

One area of concern arising from these results however, was the apparent variability in the GC/MS yields. Although the trends described above seemed to be genuine, they did not appear to be smooth, consistent, or of great magnitude.

4.1.7 Phosphine screen

Having identified the "best-case" conditions for further investigations, the next step was to examine the effect of the phosphine co-catalyst. It was expected that the transmetallation of the aryl group from germanium to palladium would be the ratelimiting step, and consequently, it was hoped that a careful choice of ligand could exert a large effect on the reaction.



Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (5mol% Pd), phosphine (10mol%), DMF, 150°C, 48h.

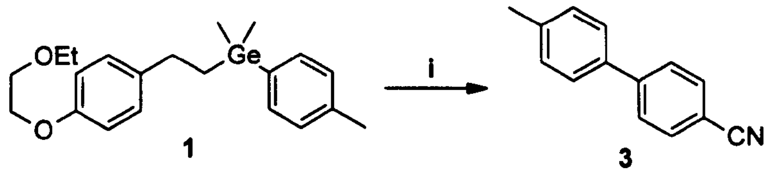
Phosphine	GC/MS yield
PPh_3	0.7%
P(*o*-Tol)$_3$	Not observed
P(2-Furyl)$_3$	0.1%
P(*p*-C_6H_4F)$_3$	0.4%
P(*p*-$C_6H_4CF_3$)$_3$	0.1%
$P(C_6F_5)_3$	0.3%
P(Mes)$_3$	0.1%
PPh_2(2-Pyridyl)	Trace
Dppe	0.4%
Dppp	1.1%
Dppf	0.1%
Binap	0.8%
PCy_2(*o*-biphenyl)	Not observed
P(OEt)$_3$	Not observed
P(t-Bu)$_3$	Not observed

Figure 4.15: Phosphine co-catalyst screen

The results from the phosphine screen were disappointing. The moderate yields from previous experiments (*i.e.* up to 33%) were irreproducible (*cf.* 0.7%). Only one phosphine, dppp, offered any improvement over the PPh_3 control experiment, although several seemed to have comparable reactivity; P(*p*-C_6H_4F)$_3$, $P(C_6F_5)_3$, dppe and binap. The improvements offered by dppp, and to a lesser extent binap, may be related to the bidentate nature of these ligands. A bidentate ligand will force the catalytic species to adopt a *cis* conformation at all times, will assist reductive elimination, and may significantly alter the mechanism of the transformation by reducing, if not eliminating, the need for *trans* to *cis* isomerisations during the catalytic cycle.

4.1.8 Experiments in an inert atmosphere

The results from the phosphine screen highlighted concerns over the reproducibility of the coupling reactions. GC/MS yields of 28-33% had been obtained on four separate occasions in the initial scanning experiments (fluoride screen figure 4.10, experiments with tolylgermane **1** figure 4.11, and experiments with anisylgermane **13** figure 4.12), including an isolated yield of 22% in the fluoride screen (figure 4.10). During the scanning experiment however GC/MS yields had been as low as 0.7% (figure 4.12), and during the phosphine screen GC/MS yields were consistently at the sub 1% level (figure 4.15). The irreproducibility was not easily explained and one possibility was that it was related to the experimental method. Experiments up to this point had been carried out in reaction vials, and as such were neither strictly anhydrous nor in a rigorously inert atmosphere. There was concern that this could be affecting the reaction, possibly by allowing poisoning of the catalyst. Another possible introduction of error was the difficulty in accurately weighing the small masses of catalyst being used (*ca.* 6mg $Pd_2(dba)_3$, 7mg PPh_3). In order to determine if this was having an effect it was decided to repeat some of the couplings in a rigorously inert and anhydrous system with a larger catalyst loading. Two identical experiments were carried out, one of which was degassed with a repeated freeze-pump-thaw cycle to remove dissolved oxygen.



Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (20mol% Pd), PPh_3 (40mol%), DMF, 150°C.

Reaction	Degassed	GC/MS yield after 1 hour	GC/MS yield after 24 hours
1	No	1.3%	1.3%
2	Yes	1.9%	1.9%

Figure 4.16: Cross-couplings in an inert atmosphere

The results from these experiments confirmed that the GC/MS yield of 33% in the scanning experiment was irreproducible. The problem with the reaction was not related to catalyst poisoning, as an inert atmosphere and a degassed reaction solvent had made little if any difference compared to the less rigorously controlled experiment. Similarly, the higher catalyst loading (20mol% Pd, *cf.* 5mol% Pd for previous experiments) did not appear to have made any significant difference.

The one very intriguing result that was revealed by these experiments was the fact that whatever reaction was occurring was taking place in the first hour of heating. In order to investigate this further it was decided to look at the reaction yields varied as a function of the reaction temperature and duration.

4.1.9 Time-temperature experiments

As in the inert atmosphere experiments described above, it was decided to carry out this study in a round bottom flask rather than a reaction vial. The reagents were combined and placed in an inert atmosphere prior to heating and monitoring as a function of time.

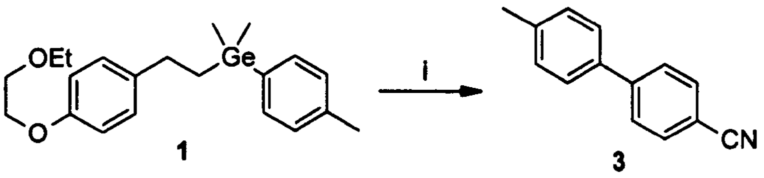


Figure 4.17: Time-temperature variable cross-coupling experiments

Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (20mol% Pd), PPh_3 (40mol%), DMF, 150°C.

The reaction was initially heated at 80°C and sampled after 1 and 2 hours, the temperature was raised to 100°C and the reaction again sampled after a further 1 hour. Finally, the reaction was raised to 120°C and then sampled after another hour, and after 17 hours, making a total reaction time of 21 hours (figure 4.18).

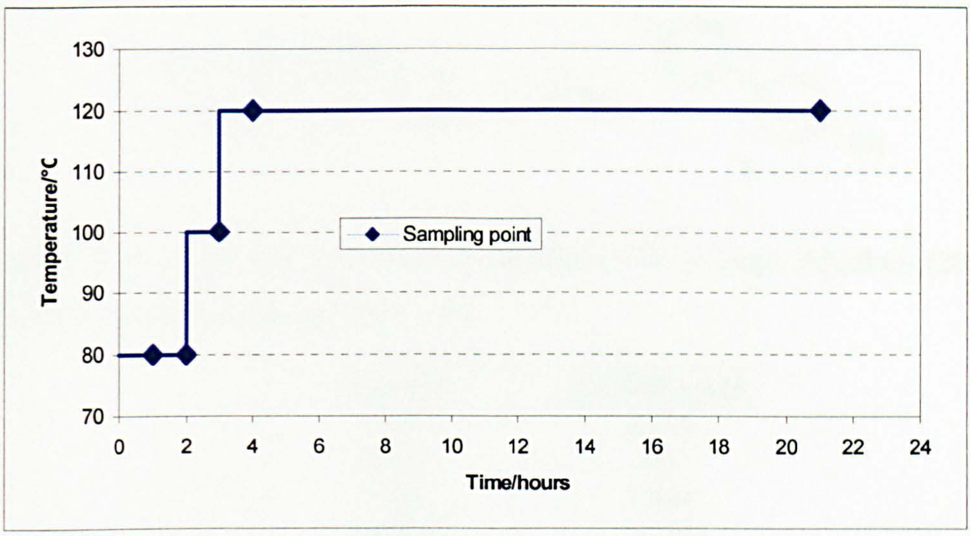


Figure 4.18: Variation of temperature and time of sampling points

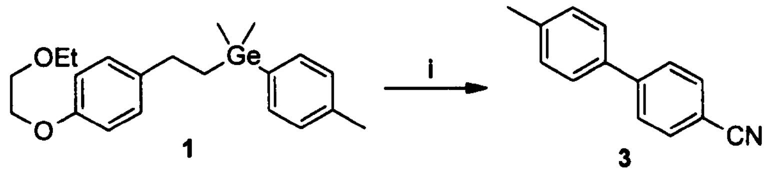
Temperature	Time	GC/MS yield
80°C	1h	0%
80°C	2h	0%
100°C	3h	0%
120°C	4h	0.1%
120°C	24h	0.1%

Table 4.3: GC/MS yields for time-temperature cross-coupling experiments

These results confirm the hypothesis that a reaction takes place rapidly once a threshold temperature is reached. No reaction whatsoever occurs below 120°C.

4.1.10 Solvent screen

Having investigated fluoride activators and phosphine variables, and having looked at couplings in an inert atmosphere the next variable for consideration was the solvent. A wide range of solvents was investigated, including polar, non-polar, coordinating and non-coordinating solvents.



Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (20mol% Pd), PPh_3 (40mol%), solvent, 150°C, 24h.

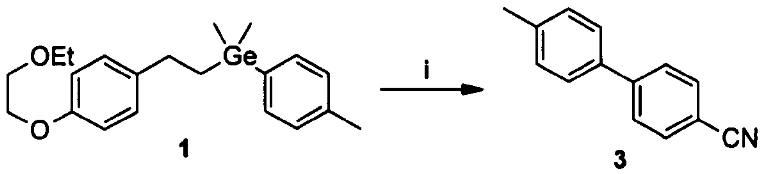
Solvent	**GC/MS yield**
DMF	1.0%
DMA	4%
NMP	Trace
MeCN	0.1%
DMSO	Trace
THF	Trace
1,4-Dioxane	Trace
1,2-Dimethoxyethane	0.1%
Toluene	Trace
Pyrrolidine	Not observed

Figure 4.19: Solvent screen

Again, few of the solvents tried offered any significant improvement over the use of DMF, however, DMA did give a relatively dramatic 4% yield compared to the 1% yield from the control experiment with DMF as solvent.

4.1.11 Biphasic reactions

As an extension to the solvent screen, tolylgermane **1** was exposed to typical phase-transfer Suzuki coupling conditions.[1,185]

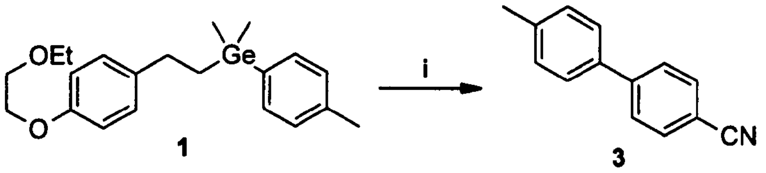


Reagents and conditions: i) 4-bromobenzonitrile, $Pd_2(dba)_3$ (20mol% Pd), PPh_3 (40mol%), toluene, EtOH, aqueous activator (2eq), 115°C, 17h.

Activator	GC/MS yield
KOH	0.3%
NaOAc	Trace
$TBAF \cdot 3H_2O$	Trace

Figure 4.20: Biphasic reaction conditions

The reaction was then attempted using $Pd(PPh_3)_4$ as the catalyst to determine whether the $Pd_2(dba)_3/PPh_3$ combination used previously was comparable to $Pd(PPh_3)_4$, which is known to be a successful catalyst under Suzuki conditions *(vide supra)*.



Reagents and conditions: i) 4-bromobenzonitrile, catalyst (20mol% Pd), toluene, EtOH, aqueous activator (2eq), 115°C, 17h, GC/MS yield 0.1%.

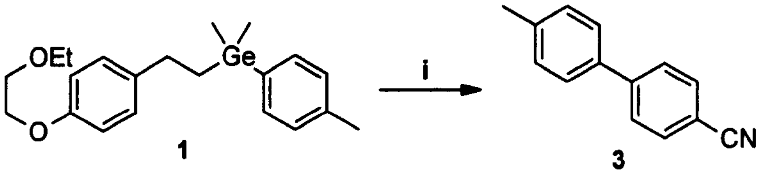
Activator	Catalyst	GC/MS yield
KOH	$Pd(PPh_3)_4$	0.1%
Degassed KOH	$Pd_2(dba)_3 + PPh_3$ (40mol%)	Trace
Degassed CsF	$Pd_2(dba)_3 + PPh_3$ (40mol%)	Trace

Figure 4.21: Further biphasic reaction conditions

These results merely served to confirm that both $Pd_2(dba)_3/PPh_3$ and $Pd(PPh_3)_4$ possessed similar catalytic ability; namely that neither gave any significant cross-coupling activity under Suzuki conditions, and furthermore that degassed bases made little, if any, difference to the coupling.

4.1.12 Activator screen

The final variable that could be expected to make a significant difference was the activator. The assumption had been that fluoride would be the most appropriate activator for germanium, as both silicon and tin are known to be highly fluorophilic due to the thermodynamic preference for forming the extremely strong metal-fluoride bond. As a result of this fluoride has been the activator of choice for silicon and tin (*vide supra*). However, results to this point had not provided unequivocal evidence that fluoride was the activator of choice for germanium, and furthermore the formation of germanium-oxygen bonds is also known to be highly thermodynamically favourable.[186] With this in mind it was felt necessary to investigate the use of non-fluoride activators to see if nucleophilic oxygen or nitrogen compounds could effect cross-coupling.



Reagents and conditions: i) 4-bromobenzonitrile, activator (2.2eq), $Pd_2(dba)_3$ (20mol% Pd), PPh_3 (40mol%), DMF, 150°C, 24h.

Activator	GC/MS yield
-	0.5%
CsOH	Trace
NaOMe	0.1%
H_2O_2/LiOH	Not observed
H_2N-OH.HCl/NEt_3	0.1%
DMAP	0.2%
DABCO	Trace
Pyrrolidine	0.1%
Ag_2O [(a)]	0.1%

(a): 4-iodobenzonitrile was used in place of 4-bromobenzonitrile[90]

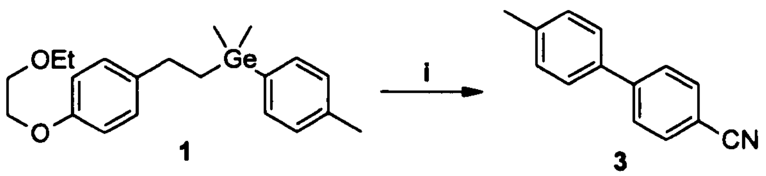
Figure 4.22: Investigation of non-fluoride activators

The use of different activators did not lead to any improvement in cross-coupling activity, with the reaction remaining stubbornly irreproducible when compared to the moderate yield observed in the fluoride screen and scanning experiments. The fact that the control experiment in the *absence* of any activator actually gave the highest GC/MS yield in this screen suggested that the germanium centre could be "tin-like", and be capable of participating in a cross-coupling reaction without an activator. Another possibility was that the two equivalents of activator were over-activating germanium and giving a coordinatively saturated hexavalent germanium species unable to react with a palladium electrophile in the transmetallation step.

One intriguing finding from these experiments was that in the absence of an activator tolylgermane **1** is *not* observed in the crude product GC/MS chromatogram. This was in marked contrast to experiments using an activator, where the arylgermane (**1**, **13**, and **16**) has been present in large amounts according to the GC/MS results. This implies that an activator perhaps either inhibits consumption of the starting material, or stabilises the arylgermanes, thereby preventing decomposition under the reaction conditions.

4.1.13 Phosphine screen in the absence of activators

As a result of the *relatively* high GC/MS yield in the absence of cesium fluoride (figure 4.22), and the possibility of an increased consumption of the starting arylgermane, it was decided to repeat a limited phosphine screen to see if the catalytic species could be optimised to give increased reactivity in the absence of an activator. The effect of DMA as solvent in the absence of activator was also considered, as was the use of the more nucleophilic anisylgermane **13**. The use of a sub-stoichiometric amount of activator was also investigated, to rule out the possibility of over-activated, unreactive hexavalent co-ordinately unsaturated germanates being formed in solution.



Reagents and conditions: i) 4-bromobenzonitrile, $Pd_2(dba)_3$ (20mol% Pd), PPh_3 (40mol%), DMF, 150°C, 24h.

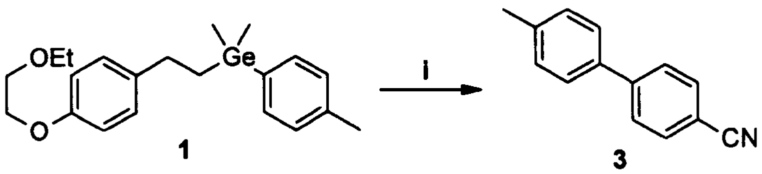
Phosphine	**Other variables**	**GC/MS yield**
PPh_3	-	0.4%
$P(p\text{-}C_6H_4F)_3$	-	0.9%
$P(C_6F_5)_3$	-	Trace
Dppp	-	0.8%
Dppe	-	0.3%
Binap	-	3%
PPh_3	DMA solvent	0.5%
PPh_3	Anisylgermane (**10b**)	3%
PPh_3	0.2eq CsF activator	1.5%

Figure 4.23: Phosphine screen in the absence of activators

No significant increase in cross-coupling reactivity was noted in any of these experiments, although the superiority of DMA over DMF was reinforced, as was the increased nucleophilicity and hence marginally increased activity of anisylgermane **13** over tolylgermane **1**. A sub-stoichiometric amount of activator seemed to give a slightly greater amount of desired product, but the yield certainly remained of the same order of magnitude as that for reactions both with and without activator.

4.1.14 "Best-case" coupling

In order to give some validation to the work that had been carried out so far, the best combination of reagents and starting materials were combined and subjected to cross-coupling conditions.



1

3

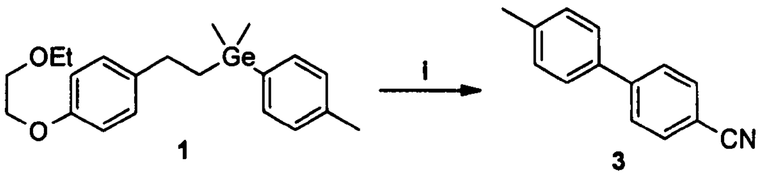
Figure 4.24: "Best-case" coupling conditions

Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (20mol% Pd), dppp (40mol% P), DMA, 150°C, 24h, GC/MS yield 4%.

Somewhat gratifyingly, the best observed conditions from the screening experiments did give the highest GC/MS yield seen since the scanning experiment. Nevertheless, the yield in this case was still incomparable to the GC/MS and isolated yields observed during the fluoride screen (figure 4.10 and table 4.2) and the initial scanning experiment (figures 4.11, 4.12 and 4.13).

4.1.15 Conclusions

The work carried out to this point had been unsuccessful in developing a cross-coupling protocol for organogermanes. Despite some promising results at the start the reactions displayed unaccountable and unacceptable irreproducibility. Even for the control conditions coupling tolylgermane **1** with benzonitrile **2** the yields obtained were highly variable.



Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (5mol% or 20mol% Pd), PPh_3 (10mol% or 40mol%), DMF, 150°C, 24h or 48h.

Experiment	Figure	GC/MS yield
Initial fluoride screen	4.10	7.4%
Scanning experiment	4.11	33.2%
Phosphine screen	4.15	0.7%
Inert atmosphere	4.16	1.3%
Solvent screen	4.19	1.0%

Figure 4.25: Irreproducibility in control coupling experiments

This irreproducibility remained a grave concern and a significant impediment to the development of a successful cross-coupling reaction of organoarylgermanes.

The extensive reaction screening carried out had looked at every major variable in the reaction conditions, yet had failed to delineate conditions for a successful cross-coupling reaction. It was concluded that aryltrialkylgermanes were clearly unreactive towards cross-coupling, and that this could most likely be attributed to insufficient activation of the germanium centre, and/or inability to interact with the palladium(II) electrophile.

4.2 New approaches to organogermane cross-coupling

Group 14 organometallics that are unreactive to cross-coupling have been previously activated by the coordination of a nucleophile to the metal centre. The formation of the resulting pentavalent (or hexavalent) metal anion increases the partial positive charge on the metal. Crucially, this is also accompanied by an attendant increase in the partial negative charge on the axial ligand centres α to the metal.[118] It is this increase in the ligand's partial negative charge which improves its nucleophilicity, and thereby its reactivity towards an electrophilic arylpalladium(II) species. The coordination of a nucleofugal group to the metal centre will also facilitate further coordination to the metal centre, and will stabilise any developing negative charge in the transition state

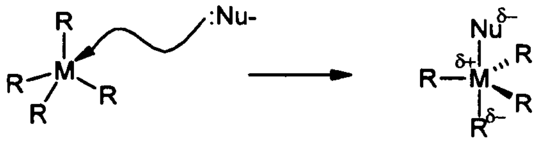


Figure 4.26: Coordination of a nucleophile increases negative charge α to the metal

Three methods have previously been used to form hypervalent metal centres in order to overcome a lack of reactivity in cross-coupling reactions:

1. Addition of an intermolecular nucleophilic activator to the reaction mixture
2. Installation of a pendant intramolecular activator within the organometallic species
3. Pre-activation by modifying the electronic properties of the metal centre to make coordination of an intermolecular activator a more favourable process

The first approach is essentially that which has been explored, without success, in section 4.1. The second approach has been previously used with Ge (figure 1.66), Sn (figure 1.6) and recently Si (figure 1.38), whilst the third avenue of investigation has until recently been the most common method of activating organosilanes, as outlined in section 1.3. Potential applications of the latter two approaches in the context of a germanium-based linker are detailed below.

4.2.1 Pendant intramolecular activation of organogermanes

The use of carbastannatranes, intramolecularly coordinated organostannanes, carbagermatranes and germatranes in cross-coupling chemistry has been presented in chapter 1. Further to these approaches however, there is very little known about organogermanium cross-coupling reactions. A germatrane would be too unstable and would be an unsuitable starting point for incorporation into a linker molecule due to the potential ease of degermylation and loss of the library molecule. Carbagermatranes however could provide a useful template for the design of a new linker.

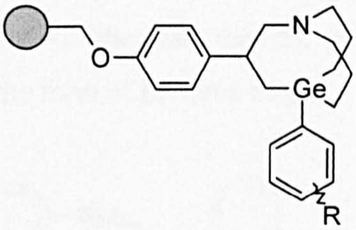
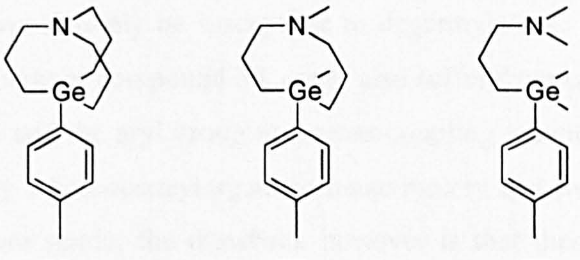


Figure 4.27: Possible carbagermatrane based linker.

However, as highlighted previously, the synthesis of carbagermatranes is non-trivial, and consequently less elaborate analogues that retain the favourable coupling characteristics would be more attractive. In order to probe the effect of intramolecular coordination on germyl cross-couplings the following molecules were considered as interesting systems that could be used to investigate the cross-coupling reactivity of arylgermanes with varying degrees of intra-molecular coordination.

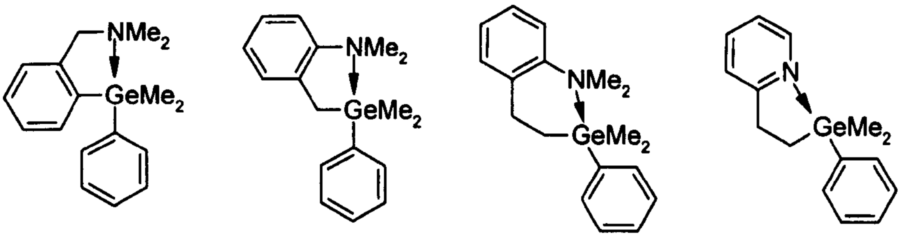


34 35 36

Figure 4.28: Proposed carbagermatrane test system, and analogues

Carbagermatrane **34** is the tolyl analogue of the phenyl molecule successfully employed by Kosugi,[129] whilst compounds **35** and **36** could be used to probe whether the rigorous control of intramolecular geometry imposed by the carbagermatrane is necessary for a reaction to occur.

A practically useful intramolecular nucleophile would probably be attached by a single tether (**36**) rather than two or three tethers (**35** or **34**). However, the effectiveness of a pendant nucleophile is likely to be reduced by increasing degrees of freedom between the Lewis acidic metal centre and the Lewis basic nucleophile. In light of this compromise, it is possible that compound **36** would actually be insufficiently reactive. If this was the case, then the problem could be addressed by introducing unsaturation in the form of benzene rings:



37 **38** **39** **40**

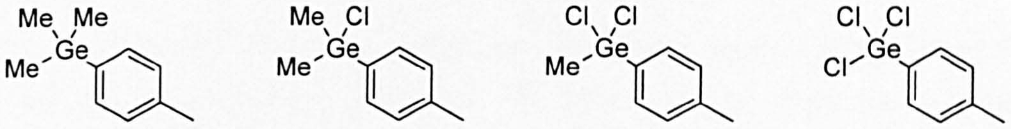
Figure 4.29:Single-tether organogermanes for cross-coupling testing

Of these compounds, **39** and **40** are perhaps the most interesting. In compounds **37** and **38** the metal and the activator are linked by aryl and benzyl organogermanes respectively. Compounds of these types are often unstable to acids and other electrophiles, and would likely be susceptible to degermylation. In addition to this, compound **37**, and perhaps compound **38**, could also suffer from competition between the linker backbone and the aryl group in a cross-coupling reaction. Compounds **39** and **40** are linked by a homobenzylorganogermane moiety and would be expected to be considerably more stable; the drawback however is that these compounds have more degrees of freedom between the Lewis acidic and basic sites of the molecule.

It was decided not to pursue this area of research, as it appeared more complex and, less synthetically accessible than the alternate approach of modifying the electronic characteristics of the germanium centre. This area of study is however being investigated in the group (Joseph Hannah, Spivey Group, 2002 to the present day).

4.2.2 Pre-activation of organogermanes

Typical pre-activation approaches with silicon have used the incorporation of halo or alkoxy groups at the silicon centre. It is known that hetero substituted germanes can be easily transformed into chlorogermanes by the action of c.HCl (*vide supra*). It was envisaged that the effects of pre-activating the germanium centre could be investigated using the following chlorogermane derivatives:



41 **42** **43** **44**

Figure 4.30: Proposed chlorogermanes for testing cross-coupling reactions

Compounds **41**–**44** were to be tested for cross-coupling activity both with and without fluoride activator. The intention of these experiments was to discover what extent of pre-activation was necessary for a successful cross-coupling reaction. Ideally, either compound **42** or **43** would prove to be an appropriate substrate as these both have scope to be incorporated into a linker *via* the remaining alkyl groups on germanium.

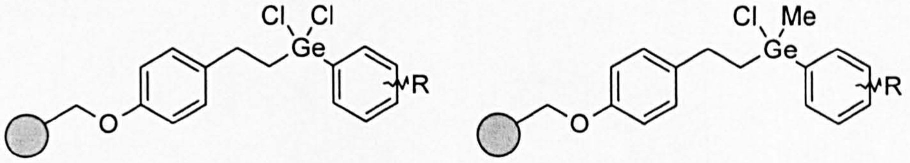


Figure 4.31: Potential incorporation of heteroatoms into an organogermane linker

Chlorogermanes and other heterogermane species are susceptible to polymerisation in the presence of water to form cyclic and linear oligomeric or polymeric germyl oxides.[186]

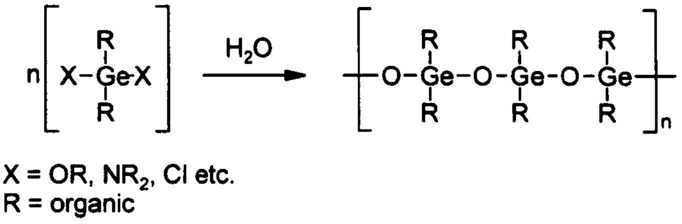


Figure 4.32: Hydrolytic polymerisation of organogermanes with hetero substituents

This reactive instability would make hetero substituted organogermanes themselves unsuitable for use as linker molecules. Consequently, it was envisaged that should this method of activation give rise to a successful cross-coupling reaction then it would be necessary to synthesise a linker molecule possessing latent functionality which would allow the selective installation of hetero atoms *in situ*. This approach would constitute a safety catch linker strategy.

For simple compounds like tolylgermanes **41-44**, trichlorotolylgermane **44** is an attractive precursor. It has been reported that trichlorotolylgermane **44** can be synthesised *via* the insertion of a dichlorogermylidene into an aryl-bromine bond.[187] Compound **41** should then be readily accessed by exhaustive methylation of this trichloride.

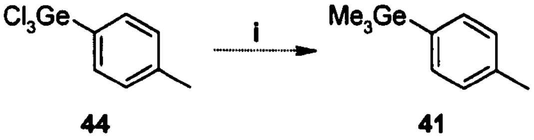


Figure 4.33: Proposed synthesis of trimethyltolylgermane

Reagents and conditions: i) MeMgBr.

It was envisaged that compounds **42** and **43** would be less trivial to make, due to the difficulty of selectively adding sub-stoichiometric amounts of organometallic reagents to chlorogermanes.[188] An inelegant, but potentially practical solution would be the addition of 1-2 equivalents of MeMgBr to trichlorotolylgermane **44**, followed by regeneration of the germanium-chlorine bonds to give a statistical mixture of compounds **41-43**. Purification could be effected either by fractional distillation of the products, or by a hydrolytic work-up to afford insoluble polymeric germyl oxides. The insoluble polymer would then be filtered to remove by-products, and the mono-, di-, and tri- oxygen substituted germanes recovered by selective rechlorination on decreasing the pH and extracting the resulting chlorogermanes into organic solution.[189]

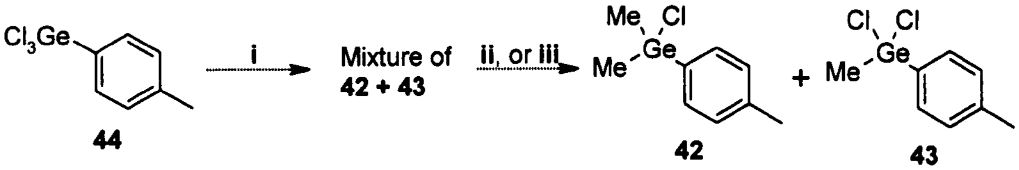


Figure 4.34: Possible syntheses of arylgermanes 9 and 10

Reagents and conditions: i) MeMgBr; ii) distillation; iii) H_2O, followed by HCl.

4.2.3 Further approaches to organogermane cross-coupling

The original hypothesis had been that germanium would behave in a "tin-like" manner, and that only an intermolecular nucleophile would be required to facilitate cross-coupling. This theory had been tested and disproved by the initial work directed at developing the cross-coupling of *dimethyl*arylgermanes (**1**, **13**, and **16**), suggesting that germanium may in fact be more like silicon, and that pre-activation of the metal centre is necessary for cross-coupling.

With this in mind, it was decided to pursue the pre-activation of organogermanes by incorporating heteroatoms at the germanium centre. It was felt that this approach would be easier to accomplish than the synthesis of either carbagermatrane **34**, and analogues **35** and **36**, or of the pendant intramolecularly activated compounds **37-40**, and would also be easier to incorporate into the current linker design.

4.3 Heterogermane cross-coupling

4.3.1 Approaches to the synthesis of trichlorotolylgermane

The crucial compound for the synthesis of germanes **41-43** was the trichlorogermane **44**. A literature synthesis of this very compound, and its tribromo analogue **45**, had been reported by Schmidbaur in 1999.[187]

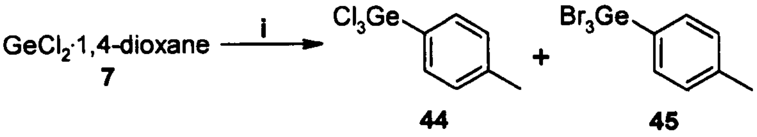


Figure 4.35: Schmidbaur's synthesis of trihalotolygermanes

Reagents and conditions: i) 4-bromotoluene, aluminium(III) chloride, 80°C, 24h, 98%.

In this reaction, 4-bromotoluene is used both as reagent and as solvent, and is present in large excess. Purification of the reaction mixture is carried out by first filtering whilst hot, to remove solid aluminium(III) chloride and germylidene starting material, and then removing bromotoluene by distillation *in vacuo*, to leave the product as a white solid. The first two attempts to replicate this work both gave rise to no observable product, with only bromotoluene being isolated. The reaction was therefore repeated at 140°C under the conditions used for synthesising trichlorogermylphenol **8**.

Proton NMR again revealed the presence of no product in the residue after distillation, but GC/MS did indicate the presence of a trace amount of trichlorogermane **44**. Correspondence with Schmidbaur revealed that the germylidene complex used by his group had been synthesised *via* reduction of germanium(IV) chloride with Et_3Si-H rather than TMDS, using a method developed by Kouvetakis.[190] It was decided to repeat the reaction using germylidene synthesised by the alternate route.

$$\underset{\mathbf{6}}{GeCl_4} \xrightarrow{i} \underset{\mathbf{7}}{GeCl_2{\cdot}1,4\text{-dioxane}}$$

Figure 4.36: Attempted synthesis of dichlorogermylidene complex

Reagents and conditions: i) Et_3SiH, $LiAlH_4$, 1,4-dioxane, toluene, 80°C for 14h, 100°C for 4-8h, 120°C for 1-2.5h.

The literature method for Kouvetakis' synthesis of germylidene 7 reported a rapid colour change after 4 hours at 100°C.[190] The first experiment was raised to 120°C after 4h at 100°C and then worked up after 1 hour, even though no colour change was observed. No desired product had been formed. Repeating the reaction at 100°C for 8 hours, and then 120°C for 1.5h still led to no colour change, but gave a 2% yield. Repeating the reaction at 120°C (2.5h), resulted in a colour change and an 18% yield (*cf.* literature 70%).[190] Despite the increased yield the compound was difficult to isolate by this method and was contaminated with small amounts of $LiAlH_4$ that could not be removed by decantation.

Despite these problems the synthesis of trichlorotolylgermane **44** was attempted using the Et_3SiH derived germylidene **7**, in conjunction with Schmidbaur's method, to give a 33% yield of the desired compound. On this occasion the presence of the reported tribromo analogue **45** was also observed. Although this represented an improvement on previous attempts, it was still incomparable to the reported 98% yield, and coupled with the difficulties in isolating both trichlorogermane **44** and the required germylidene **7** it was decided not to pursue this approach.

Another potential approach to germanes **41-44** was the selective addition of Grignard or organolithium reagents to germanium(IV) chloride or germanium(IV) ethoxide. This type of reaction is generally poorly selective, and previous work in the group with germyltrichloride **8** had led to <10% yields of the mono addition product.[188] Moderate yields have been reported using germanium(IV) ethoxide and *p*-anisyl magnesium bromide formed *in situ* (36% for mono addition, 27% for di addition).[187]

Before the addition could be investigated, it was first necessary to obtain a sample of germanium(IV) ethoxide. Surprisingly, given the proclivity of germanium(IV) chloride to polymerise and form germanium(IV) oxides in water, solvolysis does not occur between germanium(IV) chloride and ethanol. Instead, it is necessary to carry out the reaction in the presence of either an amine base to sequester HCl, or metallic sodium to pre-form the sodium alkoxide *in situ*. Owing to a simpler work up we elected to use the sodium alkoxide method.[191]

$$\mathrm{EtOH} \xrightarrow{\text{i, ii}} \mathrm{Ge(OEt)_4}$$

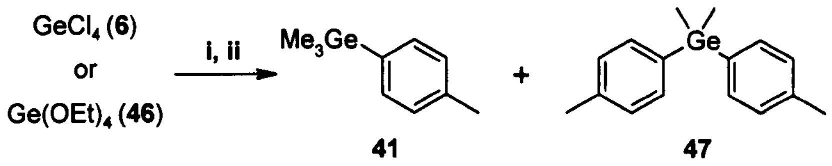
46

Figure 4.37: Synthesis of germanium(IV) ethoxide

Reagents and conditions: i) sodium metal, rt, 30min; ii) $GeCl_4$ (**6**), reflux, 3h, 27%.

The literature workup involved filtration over a pad of Celite® to remove NaCl precipitate followed by purification by distillation. The precipitate was so fine and took so long to remove by filtration that ethoxide **46** was invariably hydrolysed to the oxide before distillation could be attempted. The solution to this was to centrifuge the crude reaction mixture and decant the supernatant. Removal of the solvent *in vacuo*, followed by distillation in a Kugelrohr oven under nitrogen gave the desired product in 27% yield.

With ethoxide **46** in hand, we were then able to compare the reactivity of germanium(IV) chloride and the less reactive, therefore more selective, ethoxide **26**. In order to accurately analyse the reaction and determine the product distribution, the reaction was quenched with MeMgBr to give a mixture of predominantly the stable, isolable methylated arylgermanes **41** and **47**.



Reagents and conditions: i) *p*-TolMgBr (1eq), THF, -78°C, 1h; ii) MeMgBr, -78°C → rt over 1h, reflux 1h.

Germanium(IV) compound	^{1}H NMR Ratio of 41/47
$GeCl_4$	3.96/1
$Ge(OEt)_4$	2.74/1

Figure 4.38: Addition of Grignard reagent to germanium(IV) compounds

The ratio of products was assessed from the integrals of the germanium-methyl signals. Other impurities included bitolyl resulting from homo-coupling of the Grignard reagent present in both samples, and a small amount of tritolylmethylgermane present in the $GeCl_4$ reaction mixture. Unexpectedly, the addition to the chloride was more selective than to the ethoxide, but both ^{1}H NMR and GC/MS analysis indicated that the chloride reaction mixture contained many more impurities than the ethoxide reaction mixture. No further work was carried out to improve the selectivity in either of these reactions, although it is possible that the less reactive *iso*-propoxide, *sec*-butoxide or *tert*-butoxide analogues would give cleaner, more selective reaction mixtures.

4.3.2 Synthesis of linker related chlorogermanes

4.3.2.1 Precedent for the synthesis of linker related chlorogermanes

At this point in time, a co-worker in the group, David Turner (Spivey Group 2000-2003), developed a new route to the linker system that allowed variation of the methyl spectator ligands on germanium.[192]

The newly developed route relied on the selective formation of a dichloroanisylgermane intermediate.

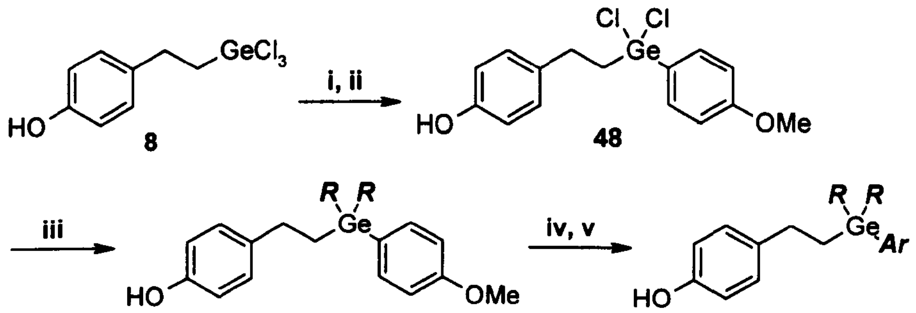


Figure 4.39: Turner's synthesis of arylgermanes with variable substitution at germanium

Reagents and conditions: i) 4-bromoanisole, Mg, THF, reflux, 17h; ii) 1M HCl/ CH_2Cl_2, followed by c.HCl, 1h, rt; iii) *R*-M, THF, reflux, 17h; iv) HCl (1.0M in Et_2O), rt, 1h; v) *Ar*-M, THF, reflux, 17h.

Trichlorogermylphenol **8** is arylated with *p*-anisyl magnesium bromide, and solvent removed *in vacuo*, before the crude reaction mixture is partitioned between dilute aqueous HCl (added slowly), and CH_2Cl_2. The layers are then separated to remove inorganic impurities. The CH_2Cl_2 layer is then further acidified with dilute HCl. It is proposed that this both removes the first anisyl group, and installs the first chloride on germanium to give a chlorodianisylgermylphenol. Concentrated .HCl is then added and the mixture stirred for 1 hour in order to remove the second anisyl group to give the dichloroanisylgermylphenol. This phenol can then be reacted with a Grignard reagent, or other organometallic (*R*-M), to introduce the desired substitution at germanium. HCl in ether is then used to smoothly remove the remaining anisyl group to give a disubstituted monochlorogermanium species analogous to chlorodimethylgermane **11**, which can be reacted with an organometallic aryl group (*Ar*-M) to give the desired linker precursor.

4.3.2.2 Synthesis of linker related chlorogermylphenols *via* selective electrophilic dearylation

For our purposes, this chemistry appeared intriguing, as it demonstrated the ability to selectively install two chlorine atoms onto an arylgermane, a solution that neatly corresponded to the problem faced in synthesising dichlorotolylgermane **43**.

Although the original intention had been to synthesise arylgermanes with methyl and chlorine substituents (**41-44**) in order to test the hypothesis that pre-activation would assist cross-coupling, proceeding directly with linker related compounds now represented a more efficient strategy.

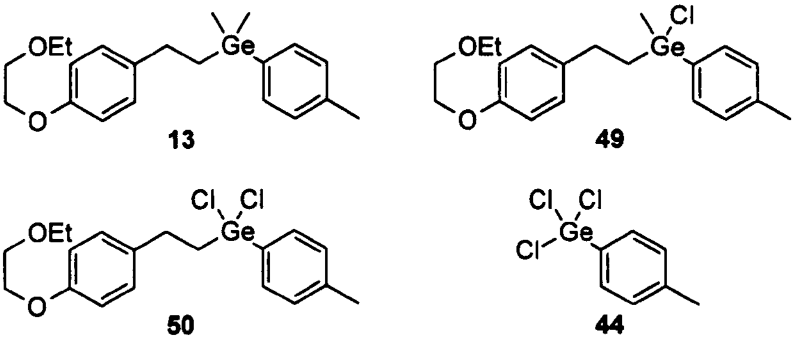


Figure 4.40: Linker related chlorogermane target compounds

Dimethyltolylgermane **1** had already been prepared, and although trichlorotolylgermane **44** was difficult to obtain as a pure compound in high yield the closely related phenyl analogue is commercially available. Of the remaining chlorogermanes **49** and **50**, dichlorogermane **50** was the obvious starting point, as it is most closely related to dichloroanisylgermylphenol **48**. Nevertheless, the synthesis of compound **50** would require some modifications to the Turner method.

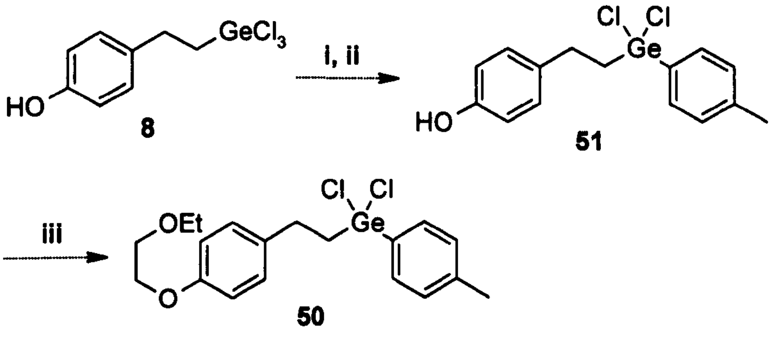


Figure 4.41: Initial synthesis of dichlorotolylgermane 50

Reagents and conditions: i) 4-bromotoluene, Mg, THF, reflux, 17h; ii) c.HCl/ CH_2Cl_2, rt, 1h; iii) 2-chloroethyl ethyl ether, Cs_2CO_3, TBAI, MeCN, 85°C, 17h.

Trichlorogermylphenol **8** was treated with a large excess of *p*-tolyl magnesium bromide before being worked up as previously described for the dichloroanisylgermylphenol **48**. The crude reaction mixture was analysed by ^{1}H NMR, and examination of the signals for the methylene groups α and β to germanium revealed the presence of two major linker related products. The chemical shifts for the β methylene groups were δ2.71ppm and δ2.81ppm, and the signals were present in a ratio of *ca.* 3/1 respectively. The chemical shift of these methylene groups is known to be affected by substitution at germanium; the corresponding trichlorogermylphenol **8** has a chemical shift of δ2.97ppm for its β methylene, whilst trimethylgermylphenol **9** has a chemical shift of δ2.51ppm for the same protons. The substitution of chlorine atoms for methyl groups at germanium shifts the methylene signals downfield.

The desired dichloride **51** was clearly not the major product of the reaction. Indeed the reaction had given either a mixture of tritolylgermylphenol (major) and chloroditolylgermylphenol (minor), or of chloroditolylgermylphenol (major) and dichlorotolylphenol (minor).

The crude reaction mixture was then split into portions for further analysis and reaction. Firstly a sample was re-subjected to a biphasic mixture of c.HCl and CH_2Cl_2, with heating to 30°C for 23 hours. On work up the ratio of products had changed from *ca.* 3/1 to *ca.* 2/3 for δ2.71ppm/δ2.81ppm, with the more highly chlorinated compound now in excess. However, it was still difficult to unambiguously determine whether the mixture corresponded to the mono- and di-chlorides, or to the tritolyl and mono-chloride.

To resolve the ambiguity, a further sample of crude reaction mixture was subjected to methyl magnesium bromide to cap any germanium-chlorine bonds present. Column chromatography was unable to separate the two resulting compounds formed, but the proton NMR of the mixture was very revealing. Firstly, there was only one signal corresponding to a germanium-methyl group, not two, and secondly the signal for one of the methylene groups β to germanium remained unchanged at δ2.75, whilst the other had moved upfield to δ2.68. The peaks remained in a *ca.* 3/1 ratio for the signals at δ2.75/ δ2.68. The major product of the reaction had not therefore been the desired dichlorotolylgermylphenol **51**, but rather tritolylgermylphenol **52**, with the minor component being chloroditolylgermylphenol **53**.

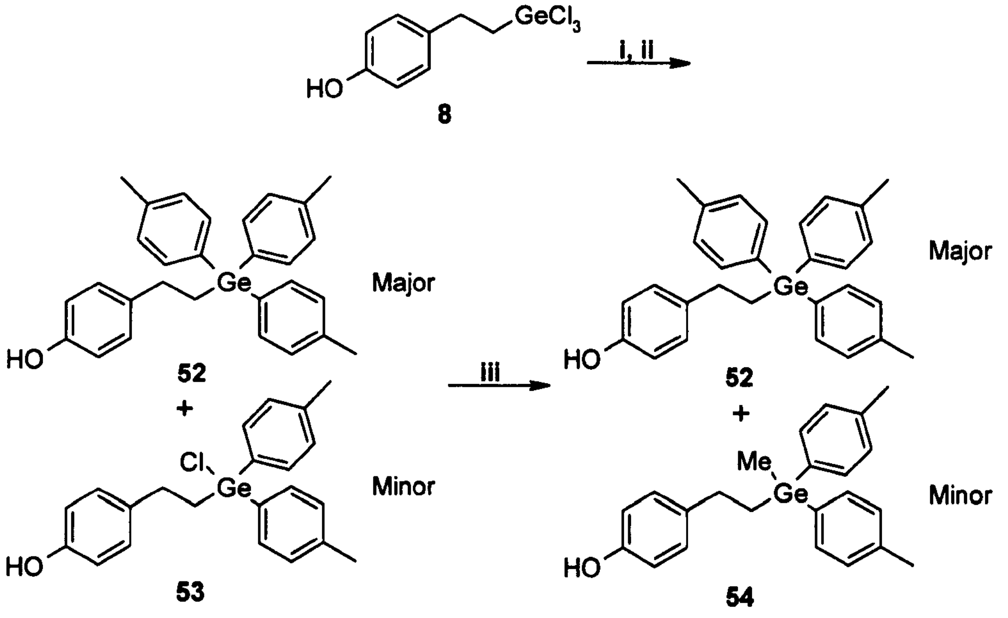


Figure 4.42: Attempted synthesis of dichlorotolylgermylphenol 31 and methyl capping of crude reaction mixture

Reagents and conditions: i) 4-bromotoluene, Mg, THF, reflux, 17h; ii) c.HCl/ CH_2Cl_2, rt, 1h; iii) MeMgBr, toluene, reflux, 17h.

A further sample of the crude reaction mixture from the attempted synthesis of dichlorotolylgermylphenol **51** was taken and subjected to a mixture of c.HCl and refluxing CH_2Cl_2 for 5 hours. Following workup, ^{1}H NMR analysis indicated that the ratio of **52**/**53** had changed to the point where chloroditolylgermylphenol **53** was the major product but remained contaminated with a trace of tritolylgermylphenol **52** (ratio of **52**/**53** *ca.* 4/96).

The use of a biphasic mixture of c.HCl and CH_2Cl_2 as the electrophilic dearylating agent had several drawbacks; the organogermane starting materials and products remained in the organic layer, whilst the electrophile was in the aqueous layer. When the mixture was heated, gaseous HCl was rapidly lost from solution, reducing the concentration of acid and thus further reducing its activity. In order to address this, a final sample of the crude reaction mixture was subjected to neat acetic acid at reflux. Although acetic acid is not as strong an acid as c.HCl, it was hoped that the increased temperature and homogeneous nature of the reaction mixture might lead to a cleaner, more selective reaction. The ratio of products, as assessed by ^1H NMR, remained unchanged by the action of acetic acid. The remainder of the crude sample from the initial reaction was purified by column chromatography and the major product unambiguously identified as tritolylgermylphenol **52**. Using this material another method to synthesise either chloroditolylgermylphenol **53**, or dichlorotolylgermylphenol **51** was attempted using c.HCl and CH_2Cl_2 in a sealed tube.

Again, although the major product after 3.5h at 45°C was chloroditolylgermylphenol **53**, some of the tritolylgermylphenol **52** remained unreacted.

It was decided at this point that c.HCl, although suitable for removing electron rich anisyl groups from germanium, was unsuitable for the clean and selective removal of tolyl groups from germanium. What was required was a strong, non-volatile acid, miscible with organic solvents. In 1994 Bardin reported several electrophilic agents, including triflic acid, capable of cleaving the electron deficient aryl-germanium bond of triethylgermylpentafluorobenzene.[193]

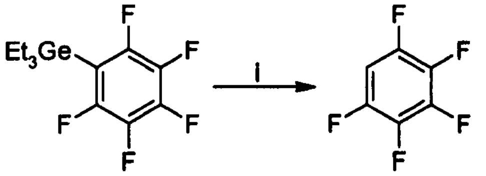
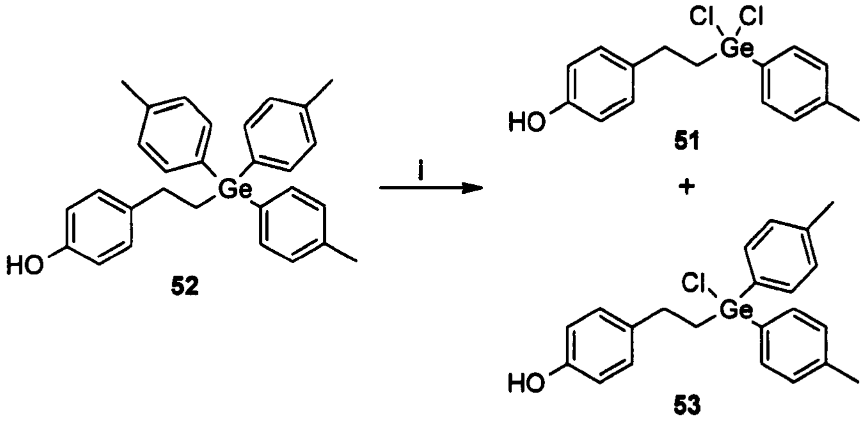


Figure 4.43: Bardin's electrophilic cleavage of triethylgermylpentafluorobenzene with triflic acid

Reagents and conditions: i) TfOH, 100%.

Acetic acid (pKa 4.76) had been shown to be unreactive towards tolyl groups, whereas triflic acid (pKa −14) was able to remove pentafluorophenyl groups. Given that a biphasic mixture of concentrated aqueous HCl (pKa –8) and CH_2Cl_2 had proven to be not quite active enough to remove a single tolyl group from germanium, it was felt that methanesulfonic acid (pKa –2.6) might be a better starting point than TFA (pKa –0.25) for further work.

Consequently, tritolylgermylphenol **52** was dissolved in CH_2Cl_2 and the resulting solution subjected to varying concentrations of methanesulfonic acid. After the time indicated, the reaction was quenched with saturated $NaHCO_3$ solution. The cleaved heterogermanes formed a white emulsion residing in the CH_2Cl_2 layer. Separation of the layers, followed by treatment of the organic layer with c.HCl gave a crude mixture chlorogermanes **51** and **53**, whose ratio was assessed by ^1H NMR.



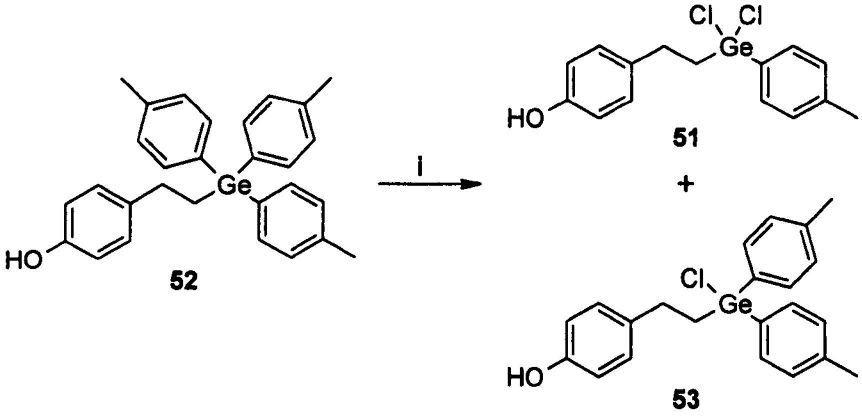
Reagents and conditions: i) MSA, CH_2Cl_2, rt.

MSA concentration	Reaction time	Product distribution: 51/53
7.7M	2min	35/65
5M	36min	53/47
2M	39min	26/74
0.23M	38min	0/100

Figure 4.44: Electrophilic dearylation of tritolylgermylphenol 52 using varying concentrations of MSA

It can be seen that a concentration of MSA of 0.23M gave desired chloroditolylgermane **53** cleanly and selectively in quantitative yield.

Now that chloroditolylgermane **53** had been successfully synthesised, attention turned to dichlorotolylgermane **51**. It was anticipated that a high concentration of MSA for an appropriate period of time should allow selective formation of the dichloride.

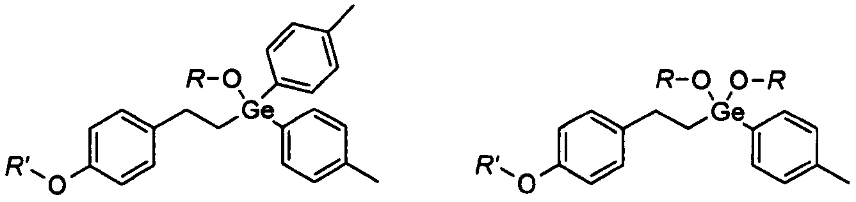


Reagents and conditions: i) MSA, CH_2Cl_2, rt.

MSA concentration	Reaction time	Product distribution: 51/53
5M	1h 4min	83/17
5M	1h 31min	89/11
2.5M	1h 31min	65/35
2.5M	2h 2min	78/22
6M	2h 30min	>99/1 (82% isolated yield)

Figure 4.45: Electrophilic dearylation of tritolylgermylphenol 52 using varying concentrations of MSA

It can be seen that the use of 6M MSA for 2.5h at rt gave the desired product cleanly, with only a trace of monochloride **53** by proton NMR. The mixture of compounds was partitioned between 0.5M aqueous NaOH and CH_2Cl_2 to give hydrolysis products **51a** and **53a** and the layers separated. Treatment of the CH_2Cl_2 layer with c.HCl regenerated monochloride **53**, whilst acidification of the base layer followed by extraction with CH_2Cl_2 gave the dichloride **51**. The solubility difference between hydrolysis products of **51a** and **53a** can be explained by the presence of the extra germanium-chlorine bond in dichlorotolylgermylphenol **51**. In the presence of base the phenol is deprotonated, and any germanium-chlorine bonds present are hydrolysed to give oligomers rather than free hydroxygermanes.[186] Hydrolysis product **51a** possesses two germanium oxygen bonds in addition to the deprotonated phenol and is water soluble, whereas the single germanium-oxygen bond in hydrolysis product **53a** is insufficient to impart water solubility on the compound.



R = H, Ge, Ar or Na$^+$
R' = Ge or Na$^+$

53a

R = H, Ge, Ar or Na$^+$
R' = Ge or Na$^+$

51a

Figure 4.46: Hydrolysis products of chlorogermylphenols 53 and 51

Chloroditolylgermylphenol **53** was capped with methyl magnesium bromide to give methylditolylgermylphenol **54**, which was then subjected to 0.23M MSA to give chloromethyltolylgermylphenol **55**.

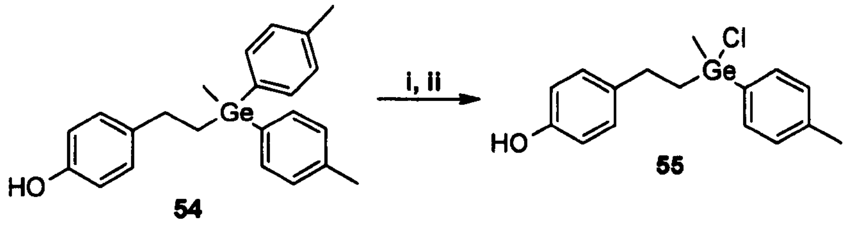


Figure 4.47: Electrophilic dearylation of methylditolylgermylphenol 32 using MSA

Reagents and conditions: i) MeMgBr, toluene, reflux, 17h, 90%.; ii) 0.23M MSA, CH_2Cl_2, rt, 99%.

Both chloromethyltolylgermylphenol **55** and dichlorotolylgermylphenol **51** were next protected as ethoxyethyl ethers *via* the same method used for protecting trimethylgermylphenol **9**.

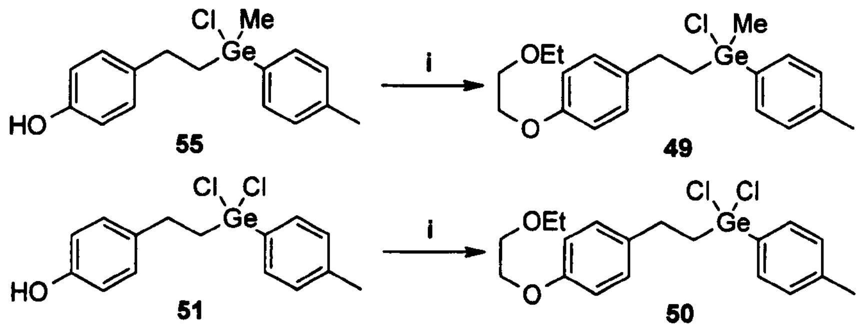
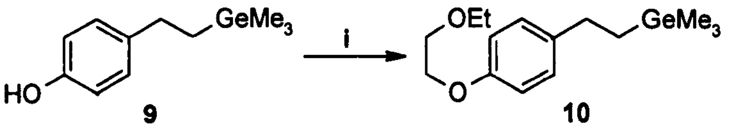


Figure 4.48: Synthesis of chlorotolylgermane solution phase models

Reagents and Conditions: i) Cs_2CO_3, TBAI (10mol%), MeCN, 2-chloroethyl ethyl ether, reflux, 17h.

In both cases the reaction failed to give pure products; starting phenol **51** or **55**, and tetrabutylammonium salts from the catalytic iodide were present in each reaction mixture. Attempts to remove the ammonium salts from either sample by extraction or filtration proved only partially successful, but dichlorogermane **50** could be separated from its starting phenol **51** by partitioning between CH_2Cl_2 and aqueous NaOH. Ether **50** remained in the organic layer, whilst phenol **51** was found in the basic layer. This approach was not successful for the separation of ether **49** from its starting phenol **55**.

To address the problem of the tetrabutylammonium salts, test reactions were carried out on trimethylgermylphenol **9** using water soluble iodide salts that could be removed by extraction.



Reagents and conditions: i) Cs_2CO_3, iodide (10mol%), MeCN, 2-chloroethyl ethyl ether, reflux, 17h.

Iodide	Yield
TBAI	92%
CsI	88%
Et_4NI	96%

Figure 4.49: Test reactions for phenol protection with alternate iodide sources

Both cesium iodide and Et_4NI successfully catalysed the reaction, and both were removed from the reaction mixture by a simple extraction between CH_2Cl_2 and water. Dichlorotolylgermylphenol **51** was then protected using catalytic Et_4NI.

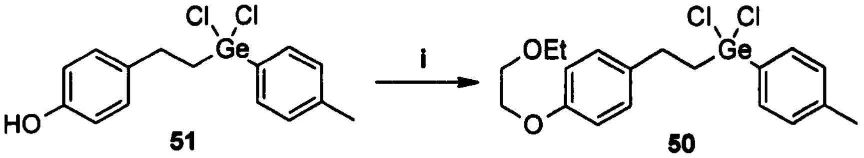


Figure 4.50: Protection of dichlorotolylgermylphenol 51

Reagents and Conditions: i) Cs_2CO_3, Et_4NI (10mol%), MeCN, 2-chloroethyl ethyl ether, reflux, 17h, 35%.

Despite the moderate yield, this approach did provide a clean sample of the desired dichlorotolylgermane **50**.

The mixture of chloromethyltolylgermanes **53** and **49** was subjected to *p*-tolyl magnesium bromide and purified to generate methylditolylgermane **56** in 75% yield from the starting chloromethyltolylphenol **53**.

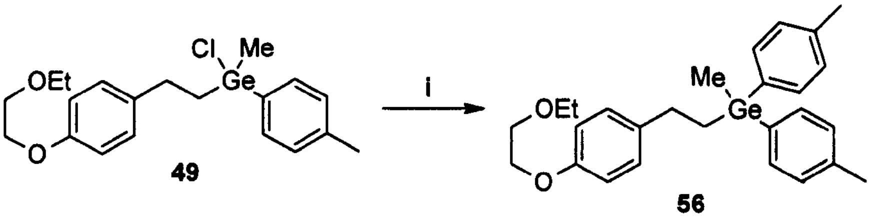


Figure 4.51: Arylation of chloromethylgermane 49

Reagents and conditions: i) *p*-TolMgBr, THF, reflux, 19h.

There had been some concern about the effect that MSA might have on the ethoxyethyl chain in the linker model compounds. Now that methylditolylgermane **56** was in hand, it was decided to attempt an electrophilic dearylation to determine if this was a feasible approach to the synthesis of chloromethyltolylgermane **49**.

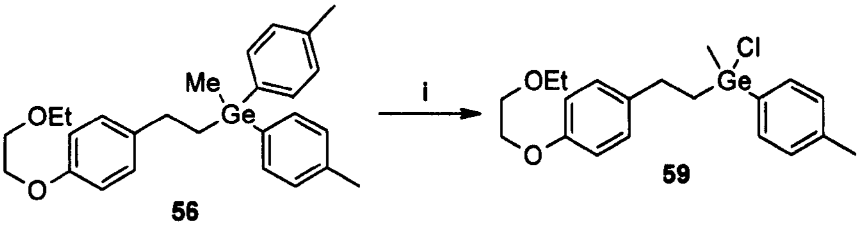


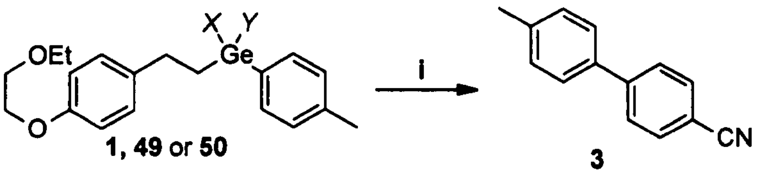
Figure 4.52: Electrophilic dearylation of methylditolylgermane 56

Reagents and conditions: i) 0.23M MSA, CH_2Cl_2, rt, 30min, 94%.

The formation of chloromethyltolylgermane **49** proceeded smoothly, and gave the desired product cleanly and in good yield.

4.3.3 Cross-coupling of chlorogermanes

Having developed syntheses of chloromethyltolylgermane **49** and dichlorotolylgermane **50** it was now possible to explore the cross-coupling chemistry of these compounds. Cross-coupling was studied using the conditions determined by the scanning experiment (figure 4.14). Each experiment was carried out twice.



Reagents and conditions: i) 4-Bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (10mol% Pd), PPh_3 (20mol%), DMF, 150°C, 48h.

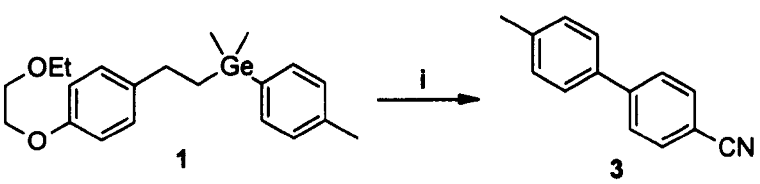
Experiment	*X*	*Y*	Germane	GC/MS yield
1	Me	Me	**1**	4%
1	Me	Cl	**49**	4%
1	Cl	Cl	**50**	0.9%
2	Me	Me	**1**	3%
2	Me	Cl	**49**	5%
2	Cl	Cl	**50**	0.5%
3	Me	Me	**1**	4%

Figure 4.53: Effect of substitution at germanium on cross-coupling

Dichlorotolylgermane **50** proved to be a poorer substrate than dimethyltolylgermane **1**, whilst chloromethyltolylgermane **49** offered only a slight improvement over dimethyltolylgermane **1**. The yield for the dimethyltolylgermane **1** (*ca.* 4-5%) was higher than had been observed previously, with the exception of the original, and unrepeatable, 33% yield (figure 4.11). Consequently, it was decided to revisit the cross-coupling chemistry of dimethyltolylgermane **1**.

4.3.4 Dimethyltolylgermane: second phosphine screen

Due to the large variation in yields between the initial scanning experiment (sections 4.1.5 and 4.1.6) and the subsequent screening experiments (sections 4.1.7 to 4.1.13) there had always been some concern as to which were the more reliable results. The apparent reproducibility of a *ca.* 4-5% yield lent credence to the idea that the yield of 33% was the outlying result, but the phosphine screening experiment had still been characterised by yields below 1%. It was decided to carry out a second screening experiment using selected phosphines



Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (20mol% Pd), phosphine (40mol% P), DMF, 150°C, 24h.

Phosphine	GC/MS yield
PPh_3	3%
Dppp	3%
$P(p\text{-}C_6H_4F)_3$	7%
$P(C_6F_5)_3$	2%
Binap	6%

Figure 4.54: Second phosphine screen

Although the GC yields obtained were consistently higher than in the previous phosphine screen (section 4.1.7) they remained too low to be practically useful.

4.3.5 Cross-coupling chemistry of furylgermanes

At this point in time Oshima published his cross-coupling studies using trifurylgermane (section 1.5.4).[135] This precedent suggested the analogous difurylgermane **57** as a potential cross-coupling reagent. It was anticipated that this compound could be synthesised from dichlorotolylphenol **51**, and indeed this was the case.

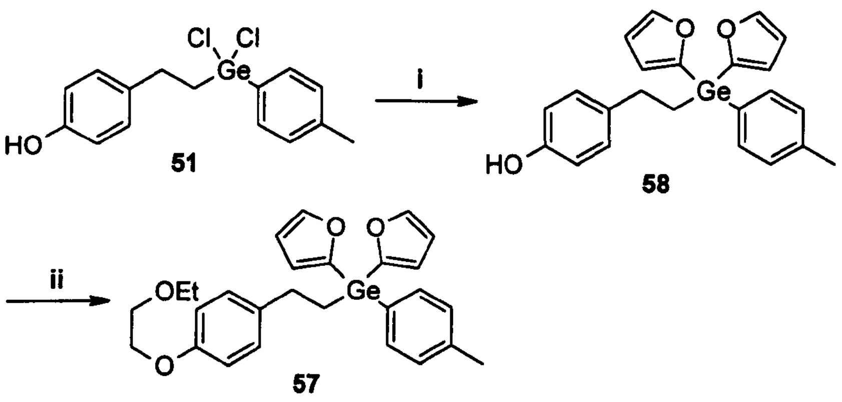


Figure 4.55: Synthesis of difurylgermane 57

Reagents and conditions: i) furan, n-BuLi, THF, 0°C, 1.5h, 39%; ii) Cs_2CO_3, Et_4NI (10mol%), MeCN, 2-chloroethyl ethyl ether reflux, 19h, 88%.

Trifurylphenylgermane **60** was also synthesised from commercial trichlorophenylgermane **59** in order to carry out control reactions.

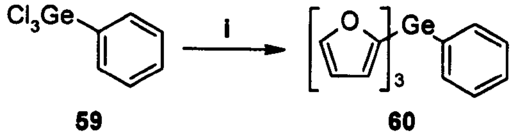
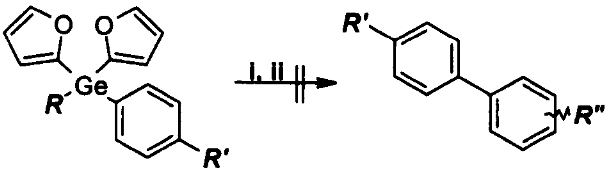


Figure 4.56: Synthesis of trifurylphenylgermane 60

Reagents and conditions: i) furan, n-BuLi, THF, 0°C, 1.5h, 81%.

Trifurylphenylgermane **60** was initially reacted with benzonitrile **2** using Oshima's conditions (although this was not one of the arylbromides Oshima used).



Reagents and conditions: i) TBAF (3eq, 1.0M in THF/H_2O), NMP, rt, 10min; ii) aryl bromide, $Pd_2(dba)_3.CHCl_3$ (10mol% Pd), P(2-furyl)$_3$ (10mol%), 100°C, 16h.

R	R'	Germane	Aryl bromide		Product	Yield
Furyl	H	**60**	4-Cyano	**2**	-	-
Furyl	H	**60**	3-Trifluoromethyl	**62**	**63**	34%
Linker	Methyl	**57**	3-Trifluoromethyl	**62**	-	-

Figure 4.57: Furylgermane cross-coupling reactions

As no coupled product was formed, trifurylphenylgermane **60** was exposed to cross-coupling, exactly as reported by Oshima, with benzotrifluoride **62**.[135] This afforded coupled product **63** in 34% yield (*cf.* 64% reported by Oshima) . However, using the same conditions difurylgermane **57** did not react. Both GC/MS and ^{1}H NMR indicated the recovery of starting material **57** (isolated in 20% yield after work up). It was concluded that, surprisingly, TBAF was not leading to hydrolysis of the germanium-furyl bonds.

In order to test this, furylgermanes **57** and **60** were reacted with TBAF in refluxing THF. Oshima had reported that trifurylgermane **60** gave the hydrolysis product **64** under these conditions, as evidenced by NMR (figure 1.72).

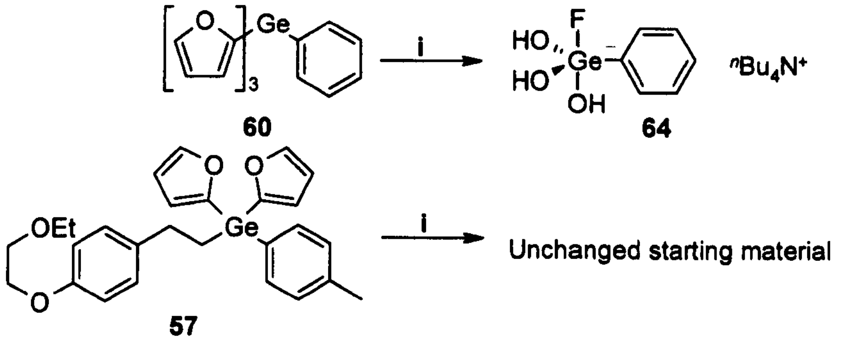
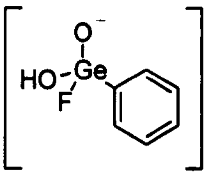


Figure 4.58: Oshima's proposed furylgermane cross-coupling intermediate, and attempted formation of the analogous intermediate for difurylgermane 57

Reagents and conditions: i) TBAF (4eq or 3eq, 1.0M in THF/H_2O), THF, rt, 3h, reflux, 4h.

The crude reaction mixtures were analysed by negative ion ESI FIA/MS. Nothing was seen for difurylgermane **57**, but, for trifurylphenylgermane **60**, a peak at *m/z* 203 was observed and *tentatively* identified as a related hydrolysis product **65**.



65

Figure 4.59: Proposed structure for trifurylphenylgermane hydrolysis product at *m/z* 203

This in itself is an interesting result, as Oshima had only used NMR data to propose the involvement of a trihydroxygermane intermediate, our mass spectrometry studies would appear to lend weight to that proposal.

The contrast in behaviour between trifurylgermane **60** and difurylgermane **57** when exposed to TBAF is dramatic; trifurylgermane **60** undergoes complete hydrolysis of the furyl-germanium bonds, behaving more like an arylsilane than an arylgermane,[194] whilst difurylgermane **57** remains unchanged.

Trifurylgermanes are however known to have anomalous characteristics when compared to other organogermanium species and one notable difference is in the polarisation of the Ge-H bond in trifurylgermane compared to a trialkylgermane.[195] In the presence of base, trifurylgermane behaves as a source of nucleophilic germanium, whereas a trialkylgermane will have a relatively electrophilic germanium centre, and will consequently act as a source of hydride.

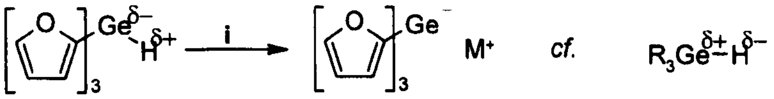


Figure 4.60: Relative polarisation of Ge-H bond in trifurylgermane and trialkylgermanes

Reagents and conditions: i) t-BuOK, DMF

Trifurylgermane also behaves atypically relative to other triorganogermanes and triorgano group 14 organometallic hydrides when it comes to Et_3B catalysed hydrogermylation of alkenes,[196] the palladium(0) catalysed hydrogermylation of alkynes and dienes,[197] and the palladium catalysed carbonylative hydrometallation of alkynes.[198] The unusual reactivity profile of trifurylgermanes has been proposed by Oshima to be explained by the large degree of pπ-dπ bonding between furyl groups (and also, thiophenyl, benzofuryl and benzothiophenyl groups) and the germanium centre.[199]

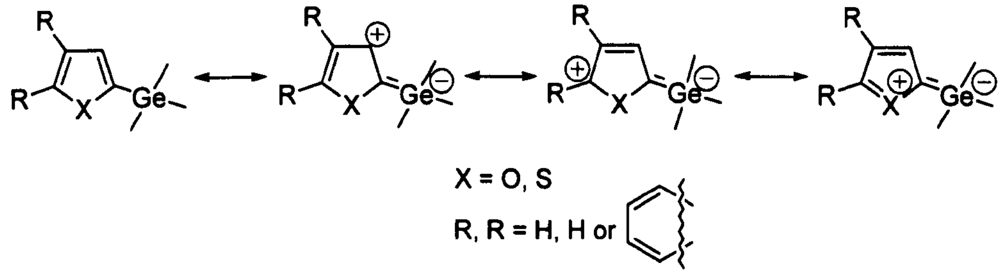


Figure 4.61: pπ-dπ Overlap between furyl, thiophenyl, benzofuryl or benzothiophenyl groups and germanium

4.3.6 Further cross-coupling chemistry of chlorogermanes

4.3.6.1 Application of Oshima's conditions to chlorogermanes

Despite the large discrepancy between the reactivity of trifuryl and difurylgermanes towards cross-coupling, Oshima's work, in conjunction with emerging work from Denmark's laboratories on the mechanism of silicon cross-couplings,[96] had clearly demonstrated the essential role of hydroxy groups on the metal centre for activation towards cross-coupling. Although difurylgermane **57** had not been a suitable precursor to a dihydroxygermane it was felt that dichlorogermane **50** would be a more labile precursor. It was therefore expected that dichlorogermane **50** would be able to smoothly form a hypervalent hydroxygermane or germoxane oligomer in the presence of TBAF and its associated water of crystallisation. To test this idea it was decided to expose dichlorogermane **50** to Oshima's cross-coupling conditions. Firstly however, a more efficient synthesis of dichlorotolylgermane **50** was required.

Following the success of the dearylation of methylditolylgermane **56** to form chloromethyltolylgermane **49**, it was decided to investigate the electrophilic dearylation of tritolylgermane **66** to form dichlorotolylgermane **50** and chloroditolylgermane **67**.

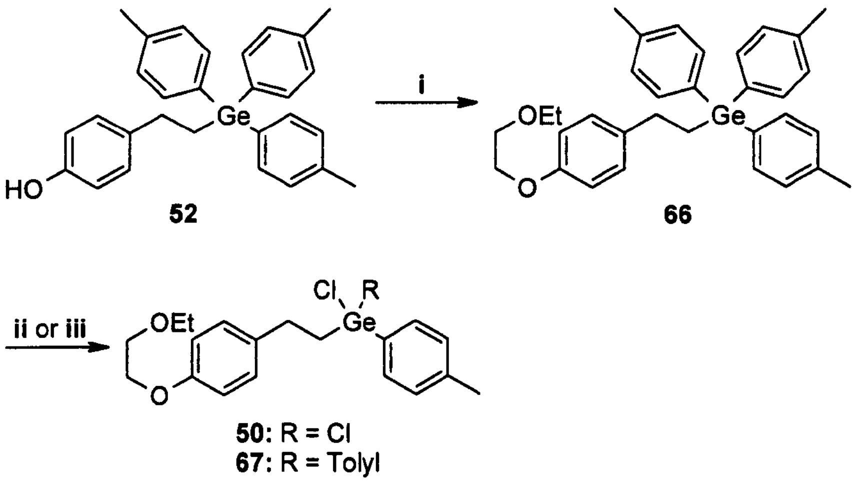


Figure 4.62: Synthesis and dearylation of tritolylgermane ether 66

Reagents and conditions: i) Cs_2CO_3, TBAI, MeCN, 2-chloroethyl ethyl ether, reflux, 17h, 90%; ii) 0.23M MSA, CH_2Cl_2, rt, 30min, to give **67** 96%; iii) 6M MSA, CH_2Cl_2, rt, 3h, to give **50** 97%.

The ethoxyethyl protection was carried out, using the same conditions as for trimethylgermane **10**, to give ether **66** in high yield. Mono and di-dearylations were carried out using the conditions applied to the synthesis of phenols **51** and **53**, and both proceeded in excellent yield. This approach offered a much simplified and higher yielding route to the desired compounds (tritolylgermylphenol **52** → dichlorogermane **50** in 87% yield, *cf.* 29% by protection of dichlorophenol **51**). Methylation of chloroditolyl ether **67** was carried out as for chloroditolylphenol **53** to give previously obtained methylditolyl ether **56** in 93% yield.

With an efficient synthesis of dichlorotolylgermane **50** now developed, the cross-coupling chemistry of chlorogermanes was revisited, initially using the method that had been successful for coupling trifurylgermane **60** and benzotrifluoride **62** (section 4.3.5).

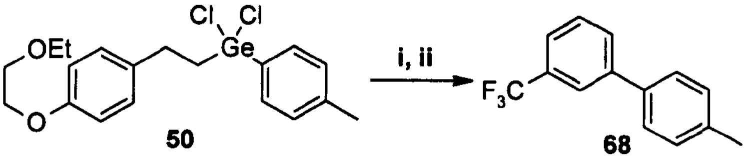


Figure 4.63: Cross-coupling of dichlorotolylgermane 50 using Oshima's conditions

Reagents and conditions: i) TBAF (3eq, 1.0M in THF/H_2O), NMP, rt, 10min; ii) 3-bromobenzotrifluoride, $Pd_2(dba)_3{\cdot}CHCl_3$ (10mol% Pd), P(2-furyl)$_3$ (10mol%), 100°C, 16h, 7%.

Disappointingly, this reaction only gave a 7% isolated yield of biaryl **68**. To form a more direct comparison with trifurylphenylgermane **60**, trichlorophenylgermane **59** was also tested as a cross-coupling precursor. This also allowed a direct comparison between dichloride **50** and trichloride **59**.

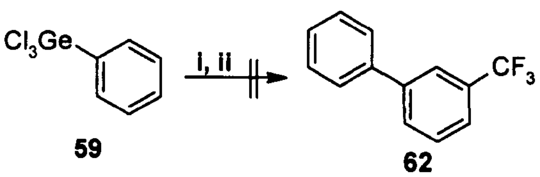


Figure 4.64: Cross-coupling of trichlorophenylgermane 59 using Oshima's conditions

Reagents and conditions: i) TBAF (4eq, 1.0M in THF/H_2O), NMP, rt, 10min; ii) 3-bromobenzotrifluoride, $Pd_2(dba)_3{\cdot}CHCl_3$ (10mol% Pd), P(2-furyl)$_3$ (10mol%), 100°C, 16h.

Trichlorophenylgermane **59** failed to react using Oshima's conditions. The disparity between this and trifurylphenylgermane **60**, which gave a 32% yield, is both counterintuitive and difficult to explain. The germanium-chlorine bonds in trichlorophenylgermane **59** will almost certainly be hydrolysed by the action of the water associated with TBAF, and should give a species very closely related, if not identical, to trihydroxygermane **64**, yet seemingly do not lead to a cross-coupling reaction. The most plausible explanation is that the large amount of chloride liberated by the hydrolysis of Lewis acidic chlorogermanes is perhaps inhibiting the reaction in some manner.

4.3.6.2 Hydroxide mediated chlorogermane cross-couplings

Having established dichlorotolylgermane **50** as a potential coupling partner, giving superior yields to previous studies, we then re-examined the literature of chlorosilane cross-couplings (section 1.3.1), especially Hiyama's 1997 report that hydroxide is a superior activator to fluoride in chlorosilane cross-couplings.[54]

Hiyama employed a long induction time, during which the activator and organometallic were pre-mixed and allowed to react together. Moreover, Hiyama also allowed the palladium and phosphine sources to be stirred for 40 minutes to allow the active catalyst species to form. Hiyama's 1997 paper contained an example of a dichloroethyltolylsilane, highly analogous to dichlorogermane **50**, undergoing cross-coupling with 3,5-bistrifluoromethylbromobenzene **69**.

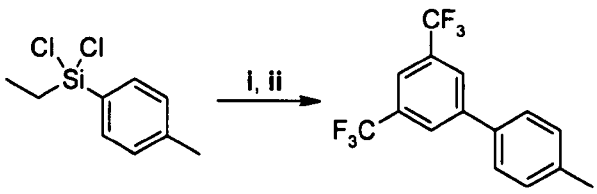


Figure 4.65: Hiyama's hydroxide mediated cross-coupling of dichlorotolylsilane

Reagents and conditions: i) NaOH (6eq), THF, rt, 3h; ii) 3,5-bistrifluoromethylbromobenzene, $Pd(OAc)_2$ (1mol%), PPh_3 (2mol%), 60°C, 39h, 85%.

This report provided an opportunity to make a direct comparison between the cross-coupling activity of organosilanes and organogermanes.

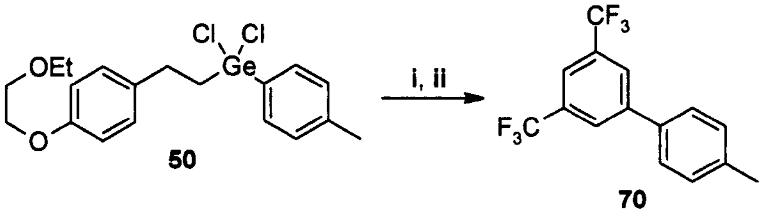
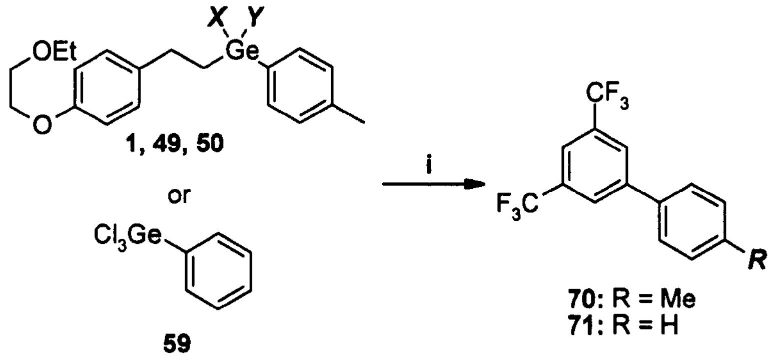


Figure 4.66: Hydroxide mediated cross-coupling of dichlorotolylgermane 50

Reagents and conditions: i) NaOH (6eq), THF, rt, 3h; ii) 3,5-bistrifluoromethyl bromobenzene, Pd(OAc)$_2$ (5mol%), PPh$_3$ (10mol%), 66°C, 24h, 32%.

Pleasingly, these conditions gave an isolated yield of 32%. Even more pleasingly, the coupling proved to be reproducible, as repeat reactions gave yields of 32% and 36%. Now that successful cross-coupling conditions had been identified, it was decided to reinvestigate the effect of substitution at germanium.



Reagents and conditions: i) NaOH (6eq), THF, rt, 3h; ii) 3,5-bistrifluoromethyl bromobenzene, Pd(OAc)$_2$ (5mol%), PPh$_3$ (10mol%), 66°C, 24h.

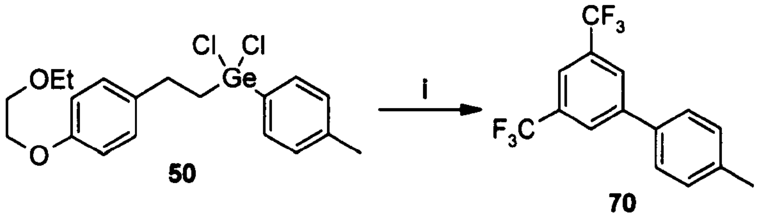
X	*Y*	Germane	Product	Yield
Me	Me	**1**	**70**	0%
Me	Cl	**49**	**70**	0%
Cl	Cl	**50**	**70**	36%
GeCl$_3$		**59**	**71**	43%

Figure 4.67: Investigation into the effect of substitution at germanium

These results show clearly the importance of the heteroatomic substitution at germanium. Both the dimethyl, and surprisingly, the chloromethylgermanes **1** and **59** respectively were unreactive and furnished no coupled product at all.

Dichlorogermane **50** gave a moderate yield, with trichloride **59** offering a slight increase in reactivity. Regardless of this, it can be seen that dichloro substitution at germanium is clearly sufficient for cross-coupling, and can be satisfactorily incorporated into a linker model compound.

In the reactions carried out so far, solid sodium hydroxide had been used as an activator. Although successful, this base is deliquescent, and consequently can absorb varying amounts of water prior to use. It was felt that this represented a potential source of irreproducibility. Hiyama had reported that aqueous sodium hydroxide could also be used. It was decided to test aqueous sodium hydroxide, the more soluble cesium hydroxide at 60°C, and also to examine Hiyama's sodium hydroxide and potassium fluoride conditions at elevated temperature (*i.e.* 120°C).[52]



Reagents and conditions: i) activator (6eq), solvent, rt, 3h; ii) 3,5-bistrifluoromethyl bromobenzene, $Pd(OAc)_2$ (5mol%), PPh_3 (10mol%), 24h.

Activator	Solvent	Temperature	Yield
NaOH (aq)	THF	60°C	Starting material + trace product
CsOH	THF	60°C	Starting material + trace product
NaOH	DMF	120°C	1,3-Bis(trifluoromethyl)benzene
NaOH (aq)	DMF	120°C	1,3-Bis(trifluoromethyl)benzene
KF	DMF	120°C	62%

Figure 4.68: Alternate activation methods

At 60°C, neither aqueous sodium hydroxide nor cesium hydroxide were successful activators, whilst at elevated temperature both forms of hydroxide activator reduced the aryl halide to 1,3-bis(trifluoromethyl)benzene. The use of potassium fluoride however led to a significantly improved reaction, giving cross-coupled product **70** in a synthetically useful yield for the first time (62%). Having established viable cross-coupling conditions that proceeded in good yield it now remained to see if the catalyst could be further optimised.

4.3.6.3 Optimisation of dichlorotolylgermane cross-coupling

Optimisation of the catalyst was approached using an array method, and reactivity assessed using ESI LC/MS. Before this could be commenced, we needed a cross-coupling product that possessed an ESI ionophore, and it was felt that acetophenone **72**, derived from bromoacetophenone **14**, would offer this.

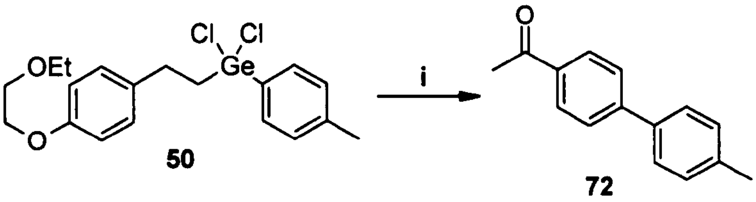
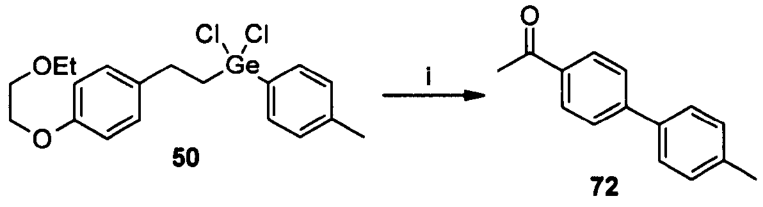


Figure 4.69: Cross-coupling of 4-bromoacetophenone

Reagents and conditions: i) NaOH (6eq), THF, rt, 3h; ii) 4-bromoacetophenone, $Pd(OAc)_2$ (5mol%), PPh_3 (10mol%), 60°C, 24h, 28%.

Using bromoacetophenone **14** and solid sodium hydroxide activator, an isolated yield of 28% was obtained (*cf.* 32-36% for 3,5-bistrifluoromethylbromobenzene). Subsequent LC/MS analysis confirmed the ability of biaryl **72** to be ionised by positive ion electrospray.

For the optimisation work, it was decided to firstly screen a series of phosphine co-catalysts under several different activator conditions using Radleys Greenhouse parallel synthesisers. Solid sodium hydroxide at 60°C and 120°C, aqueous sodium hydroxide at 60°C and 120°C, and potassium fluoride at 120°C were all tested in conjunction with eight co-catalysts. The reactivity of each individual reaction was assessed using LC peak areas. As both starting bromide **14** and starting chlorogermane **50** co-eluted under the LC conditions (see appendix 8.4) the peak area of the desired product **72** was compared to the combined peak area of *both* starting materials (**14** *and* **50**) in order to estimate the reactivity. Summation of this ratio for each variable allowed an insight into the effect on reactivity each variable was able to exert.



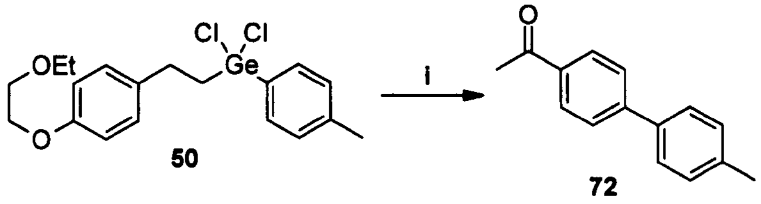
Reagents and conditions: i) activator (6eq), THF or DMF, rt, 3h; ii) 4-bromoacetophenone, $Pd(OAc)_2$ (5mol%), ligand (10mol%), 60°C or 120°C, 24h.

	NaOH (s) 60°C	**NaOH (aq) 60°C**	**NaOH (s) 120°C**	**NaOH (aq) 120°C**	**KF (s) 120°C**	**Σ**
PPh_3	-	0.12	0	0	1.19 (11%)	1.32
P(*o*-Tol)$_3$	-	0.25	1.76	0	0.29	2.30
P(2-furyl)$_3$	-	0.12	1.20	0	0.98	2.29
P(*p*-C_6H_4F)$_3$	-	0	0.59	0	1.92 (34%)	2.50
Dppp$^{(a)}$	-	0.15	0.95	0	2.21 (20%)	3.30
Dppf$^{(a)}$	-	0.20	0	0	1.09	1.29
IMes·HCl$^{(a)}$	-	0	0	0	2.11 (38%)	2.11
Ligandless	-	0	0.40	0	1.65	2.05
Σ		0.84	4.90	0.00	11.44	

Isolated yields in brackets (a): 5mol% of co-catalyst used

Figure 4.70: Peak area ratio of product/starting material for chlorogermane cross-coupling phosphine co-catalyst optimisation

As anticipated, potassium fluoride at an elevated temperature was by far the most successful activator, although it was interesting to note that sodium hydroxide at 120°C allowed some reaction with certain phosphines. For the phosphines themselves dppp, and P(*p*-C_6H_4F)$_3$ both represented a significant improvement over PPh_3. In addition to these P(*o*-Tol)$_3$, P(2-furyl)$_3$, and IMes·HCl also represented general improvement over PPh_3. However, in conjunction with potassium fluoride IMes·HCl, dppp, and P(*p*-C_6H_4F)$_3$, appeared superior to the other phosphines. It was decided to pursue the use of dppp, P(*p*-C_6H_4F)$_3$, and IMes·HCl, with PPh_3 as a control in order to carry out a screen of palladium sources.



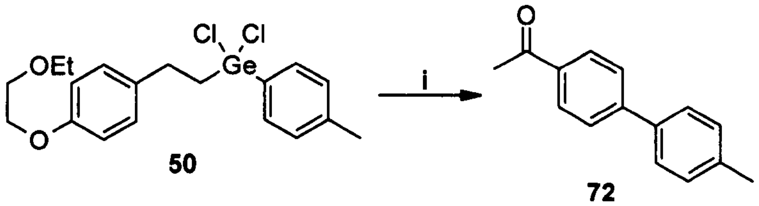
Reagents and conditions: i) activator (6eq), THF or DMF, rt, 3h; ii) 4-bromoacetophenone, Pd(OAc)$_2$ (5mol%), ligand (10mol%), 60°C or 120°C, 24h.

	Pd(OAc)$_2$	**PdCl$_2$(MeCN)$_2$**	**APC dimer**	**Pd$_2$(dba)$_3$**	**Pd(PPh$_3$)$_4$**	**Σ**
PPh$_3$	1.26	2.48	0.71	1.26	1.35$^{(a)}$	7.06
P(p-C$_6$H$_4$F)$_3$	1.53	0.48	0.82	1.52	1.65	6.00
Dppp$^{(b)}$	2.52	2.73	0.89	1.34	1.81	9.30
IMes·HCl$^{(b)}$	2.15	2.19	1.88	0.22	0.98	7.42
Σ	7.47	7.87	4.30	4.35	5.79	

Isolated yields in brackets (a): Excess PPh$_3$ was not added (b): 5mol% of co-catalyst used

Figure 4.71: Palladium source optimisation

In this screen, the pre-eminence of dppp as the best co-catalyst was reinforced. Allyl palladium chloride dimer and the two palladium(0) sources all performed poorly in comparison with palladium(II) acetate. The bis acetonitrile adduct of palladium(II) chloride, in conjunction with dppp, was marginally the best catalyst source. Reactions with Pd(OAc)$_2$, PdCl$_2$(MeCN)$_2$, PPh$_3$ and dppp were repeated on a larger scale.



50

72

Reagents and conditions: i) KF (6eq), DMF, rt, 3h; ii) 4-bromoacetophenone, Palladium (5mol%), Ligand (10mol%), 120°C, 24h.

	$Pd(OAc)_2$	**$PdCl_2(MeCN)_2$**
PPh_3	59%	50%
Dppp[a]	55%	60%

(a): 5mol% of co-catalyst used

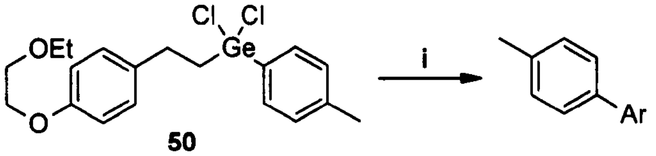
Figure 4.72: Isolated yields for best case catalyst combinations

Although the reactivity of some of these catalysts is similar, the combination of $PdCl_2(MeCN)_2$ and dppp does indeed appear to be the best catalytic system, giving an isolated yield of 60% for the coupling of dichlorotolylgermane **50** and 4-bromoacetophenone. Optimisation of the activator, the palladium source and phosphine co-catalyst, accompanied by an unoptimised change of solvent, has taken the yield of this coupling from an initial 28% up to the currently observed 60%.

One final factor to consider was the fact that use of KF instead of NaOH means that there is now no explicit water or hydroxy equivalents added to the reaction. The only water incorporated into these cross-coupling reactions is that associated with the fluoride and the solvent, as neither KF nor DMF are anhydrous, and neither were rigorously dried prior to use. In order to crudely test whether there was sufficient water present, 2 drops of distilled water were added to the reaction mixture whilst the chlorogermane precursor was being stirred with the fluoride source. The reaction gave an isolated yield of 43% of biaryl **72** (*cf.* 60% without additional water), suggesting that an *excess* of water may be deleterious to the reaction.

4.3.6.4 Examples of chlorogermane cross-coupling

With yields now at a synthetically useful level we turned our attention to an exploration of the scope of the coupling. To this end, electron deficient aryl halides **69**, **73**, **74** and **76** were selected for study.



50

Reagents and conditions: i) KF (6eq), DMF, rt, 3h; ii) aryl halide, $PdCl_2(MeCN)_2$ (5mol%), dppp (5mol%), 120°C, 24h.

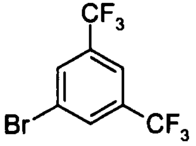
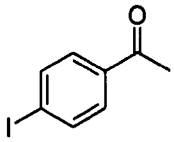
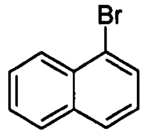
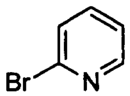
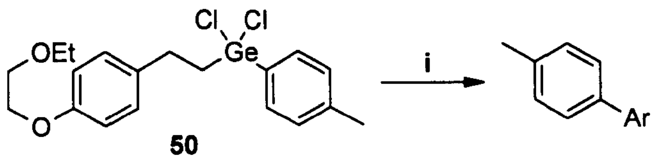
Aryl Halide		Product	Yield
	69	70	63%
	73	72	25%
	74	75	79%
	76	-	-

Figure 4.73: Cross-coupling of dichlorotolylgermane 50 with electron deficient halides

The poor yield of the aryl iodide **73** can be partly explained by the significant amount of bisacetophenyl dimer revealed by GC/MS. GC/MS analysis also indicated that pyridine **76** had failed to give any identifiable products related to the starting material. The other two examples both coupled in good yield.

Electron rich aryl halides however, did not couple successfully.



Reagents and conditions: i) KF (6eq), DMF, rt, 3h; ii) aryl halide, $PdCl_2(MeCN)_2$ (5mol%), dppp (5mol%) or IMes·HCl (5mol%), 120°C, 24h.

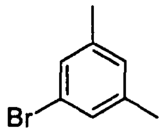
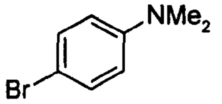
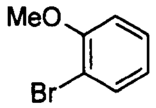
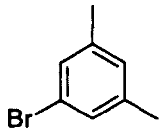
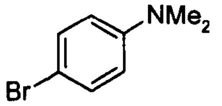
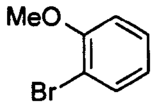
Aryl Halide		Co-catalyst	Product	Yield
	77	Dppp	-	-
	25	Dppp	-	-
	78	Dppp	-	-
	77	IMes·HCl	-	-
	25	IMes·HCl	-	-
	78	IMes·HCl	-	-

Figure 4.74: Cross-coupling of dichlorotolylgermane 50 with electron rich aryl halides

None of these examples gave any identifiable coupling products, largely due to a failure of the starting aryl halides to undergo oxidative addition. The use of the better σ-donor IMes·HCl rather than dppp did not alleviate this problem.

4.3.6.5 Synthesis and cross-coupling of anisylgermanes

The next task was to probe the effect of changing the arylgermane coupling partner. Synthesis of dichloroanisylgermane **81** was accomplished using an analogous approach to the synthesis of dichlorotolylgermane **50**.

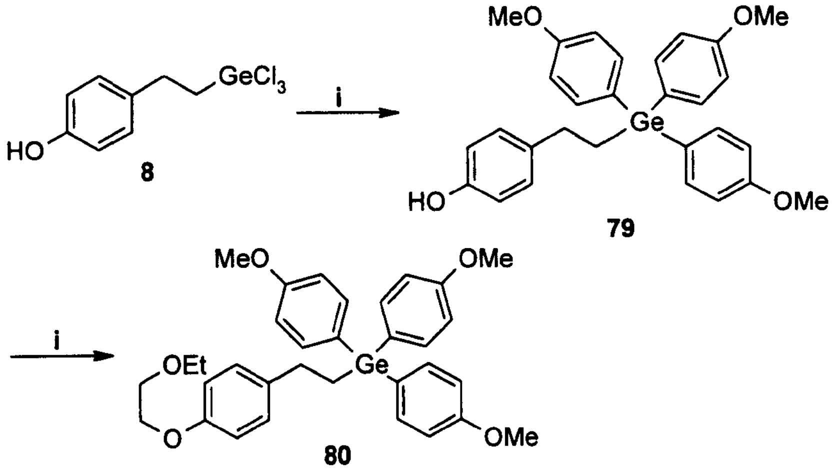


Figure 4.75: Synthesis of trianisylgermane 80

Reagents and conditions: i) 4-bromoanisole, Mg, THF, reflux, 17h, 74%; ii) Cs_2CO_3, TBAI (10mol%), MeCN, 2-chloroethyl ethyl ether, 78%.

Formation of the trianisylgermylphenol **79** took place smoothly and in better yield than the formation of tritolylgermylphenol **52**, whilst protection of the phenol afforded trianisylgermane **80**. Similarly, bis-dearylation also proceeded cleanly.

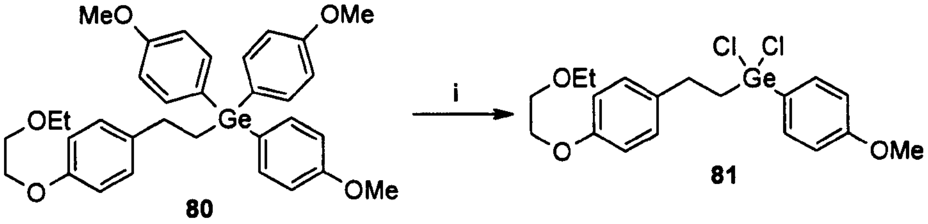
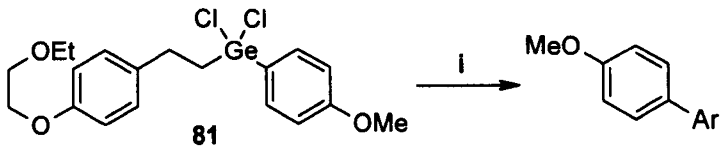


Figure 4.76: Synthesis of dichloroanisylgermane 81

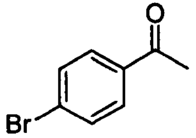
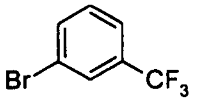
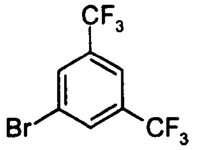
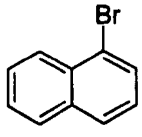
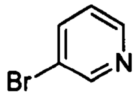
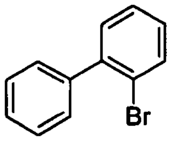
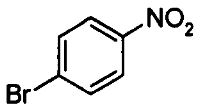
Reagents and conditions: i) c.HCl, CH_2Cl_2, rt, 3h, 82%.

Thus, using a biphasic mixture of CH_2Cl_2 and c.HCl at rt over 3 hours (*cf.* Turner's synthesis of dichloroanisylgermylphenol, section 4.3.2.1) the desired cross-coupling substrate dichloroanisylgermane **81** was obtained in good yield.

As electron rich aryl halides had failed to undergo oxidative addition when coupling with dichlorotolylgermane **50**, only electron deficient and electron neutral aryl halides were examined in conjunction with dichloroanisylgermane **81**.



Reagents and conditions: i) KF (6eq), DMF, rt, 3h; ii) aryl halide, $PdCl_2(MeCN)_2$ (5mol%), dppp (5mol%), 120°C, 24h.

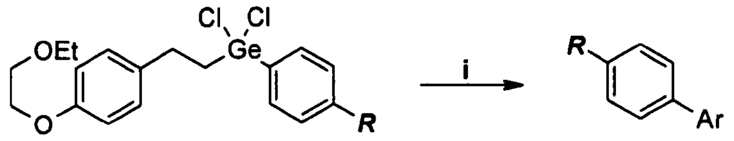
Entry	Aryl Halide		Product	Yield
1		14	85	5%
2	Ph-Br	31	20	36%
3		62	86	51%
4		69	87	71%
5		74	88	56%
6		82	89	44%
7		83	90	-(a)
8		84	91	47%

(a) 43% of aryl halide starting material recovered

Figure 4.77: Cross-coupling of dichloroanisylgermane 81

For unclear reasons bromoacetophenone **14** (entry 1) coupled in surprisingly poor yield, whilst *ortho* substituted 2-bromobiphenyl **83** (entry 7) gave 43% recovery of starting aryl bromide **83**, and an inseparable mixture of desired terphenyl **90** and homo-coupled dimers of *both* starting materials **81** and **83**. The yields ranged from good (hexafluoride **87**, entry 4, 71%) to moderate (methoxybiphenyl **20**, entry 2, 36%), with 3-benzotrifluoride (**86**, entry 3), naphthyl analogue (**88**, entry 5), and 4-nitro analogue (**91**, entry 8) being formed in yields of 51%, 56% and 47% respectively. The heteroaromatic 3-anisylpyridine **89** was formed in 44% yield (entry 6).

From this work it is difficult to draw any clear conclusions about the relative cross-coupling ability of dichloroanisylgermane **81** and dichlorotolylgermane **50**.



50: R = Me
81: R = OMe

Reagents and conditions: i) KF (6eq), DMF, rt, 3h; ii) aryl halide, $PdCl_2(MeCN)_2$ (5mol%), dppp (5mol%), 120°C, 24h.

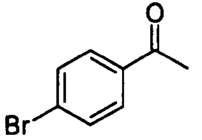
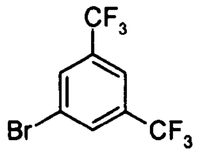
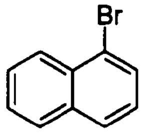
Entry	Aryl Halide		Product	Yield	
				R = Me (**50**)	*R* = OMe (**81**)
1		**14**	**85**	60%	5%
2		**69**	**87**	63%	71%
3		**74**	**88**	79%	56%

Figure 4.78: Comparison of dichlorotolylgermane 50 and dichloroanisylgermane 81

The yields for dichlorotolylgermane **50** are routinely moderate to high and are quite consistent. With the exception of bromohexafluoride **69**, dichlorotolylgermane **50** gives higher yields than dichloroanisylgermane **81**. The yields for the reactions with dichloroanisylgermane **81** are less consistent with the aryl bromides shown, particularly the anomalously low result for the coupling with bromoacetophenone **14**.

4.3.7 Synthesis and cross-coupling of germyl hydrides

Work within the group (Teyrnon Jones, Spivey Group, 2000-2004) had revealed that dimethylhydrogermanes can undergo atmospheric oxidative dimerisation in the presence of palladium.

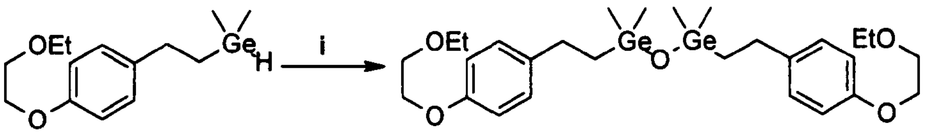
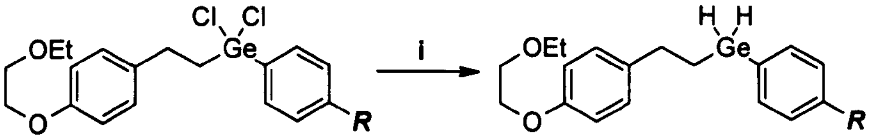


Figure 4.79: Oxidative dimerisation of hydrogermane

Reagents and conditions: i) $Pd_2(dba)_3$, non-degassed NMP, rt, 17 hours.

Considering this observation in the context of installing heteroatomic substituents onto germanium for cross-coupling, it seemed plausible that germyl hydrides might make ideal safety catch germanes for cross-coupling. To this end, dichlorotolylgermane **50** and dichloroanisylgermane **81** were both reduced with $LiAlH_4$ to give germyl hydrides **92** and **93** respectively.

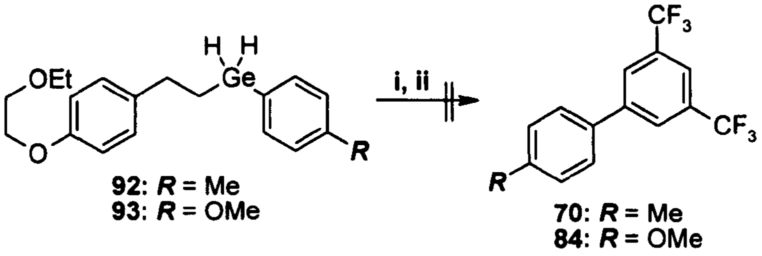


Reagents and conditions: i) $LiAlH_4$, THF, 60°C, 17h.

Starting material	R	Product	Yield
50	Me	**92**	Quantitative
81	OMe	**93**	91%

Figure 4.80: Synthesis of germyl hydrides

Both dihydrides were formed in excellent yield, and then subjected to cross-coupling using the conditions applied to dichlorogermanes **50** and **81**.



92: *R* = Me
93: *R* = OMe

70: *R* = Me
84: *R* = OMe

Figure 4.81: Cross-coupling of hydrides 92 and 93

Reagents and conditions: i) KF (6eq), DMF, rt, 3h; ii) 3,5-bis(trifluoromethyl) bromobenzene, $PdCl_2(MeCN)_2$ (5mol%), dppp (5mol%), 120°C, 24h.

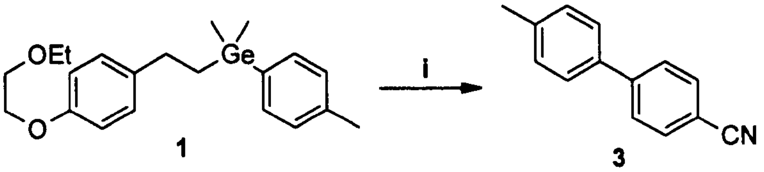
Neither system gave any discernible products related to the starting hydrogermanes or starting aryl bromide.

4.4 Conclusions

4.4.1 Reactivity of arylgermanes

The work carried out has allowed several conclusions to be drawn about the cross-coupling chemistry of arylgermanes. It would appear that aryl*dimethyl*germanes do not undergo coupling, despite the seemingly promising initial results. Instead, dichloro substitution at the germanium centre is necessary for a successful reaction.

One facet of this work that requires explanation is the variable and irreproducible level of reactivity of the aryldimethylgermanes. Early work gave a GC/MS yield of 32% and an isolated yield of 22% (section 4.1.5), the scanning experiment (section 4.1.6) gave GC/MS yields of 33% (tolylgermane **1**, bromobenzonitrile **2** and CsF), 31% (tolylgermane **1**, bromobenzene **31** and BnTMAF) and 28% (anisylgermane **13**, bromobenzonitrile **2** and CsF). The control reactions in the screening experiments routinely gave GC/MS yields at a sub 5%, or even sub 1% level for the CsF mediated coupling between tolylgermane **1** and benzonitrile **2**.



Reagents and Conditions: i) 4-bromobenzonitrile, $Pd_2(dba)_3$ (5mol% Pd), PPh_3 (10mol%), fluoride (2.2eq), DMF, 150°C, 48h.

Experiment	Conditions	GC/MS Yield	Figure
Fluoride screen	BnTMAF	31.7% (22%)[(a)]	4.10
Scanning experiment	BnTMAF	1.1%	4.11
Scanning experiment	CsF	33.1%	4.11
Phosphine screen	CsF	0.7%	4.15
Inert atmosphere	CsF	1.9%	4.16
Solvent screen	CsF	1.0%	4.19
Chlorogermane investigations I	CsF	3.9%	4.53
Chlorogermane investigations II	CsF	2.9%	4.53
Chlorogermane investigations III	CsF	3.5%	4.53

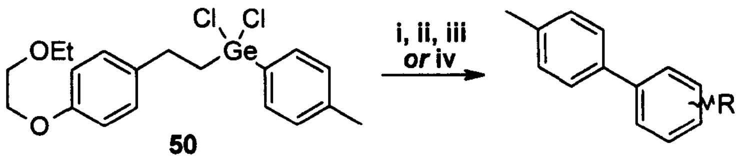
(a) Isolated yield in brackets

Figure 4.82: Variable yields of tolylgermane cross-coupling control reaction

Care was taken to exclude moisture from the reactions; however glovebox conditions were not employed and some opportunities existed for the introduction of air and water. Firstly they were carried out in sealed reaction vials; whilst the vials were oven dried, the lids could not be oven dried and the vials could not be evacuated and effectively placed in an inert atmosphere. In addition to this, all of the fluorides used, even those already hydrated, are extremely hygroscopic. Weighing under a stream of nitrogen into a sealed vial was sufficient to prevent deliquescence, but almost certainly did not prevent the absorption of some moisture.

At the time this study was commenced, the mechanism of group 14 cross-coupling was poorly developed and had only been considered as being that of a Stille-type process, and the importance of water in silicon or germanium cross-coupling reactions was not suspected. Since then, much work has been carried out that has detailed the crucial role played by water or hydroxide in Hiyama-Denmark cross-coupling chemistry.[85,96,135] In light of these reports it seems plausible that water is an essential reagent for tetra-organogermane couplings, and that the variable yields could be attributable to the absorption of varying amounts of atmospheric moisture in each reaction.

Chlorogermanes however, have been shown to be competent cross-coupling substrates, giving synthetically useful yields. It is noteworthy that these couplings are highly sensitive to the conditions and reagents employed (*cf.* unsuccessful initial chlorogermane study in section 4.3.3 and the successful chlorogermane studies described in section 4.3.6).



50

Reagents and conditions: i) 4-bromobenzonitrile, CsF (2.2eq), $Pd_2(dba)_3$ (10mol% Pd), PPh_3 (20mol%), DMF, 150°C, 48h; ii) TBAF (3eq, 1.0M in THF/H_2O), NMP, rt, 10min; ii) 3-bromobenzotrifluoride, $Pd_2(dba)_3.CHCl_3$ (10mol% Pd), P(2-furyl)$_3$ (10mol%), 100°C, 16h, 7%; iii) KF (6eq), DMF, rt, 3h, then 3,5-bistrifluoromethyl bromobenzene, $Pd(OAc)_2$ (5mol%), PPh_3 (10mol%), 120°C, 24h; iv) NaOH (6eq), DMF, rt, 3h, then 3,5-bistrifluoromethyl bromobenzene, $Pd(OAc)_2$ (5mol%), PPh_3 (10mol%), 60°C, 24h.

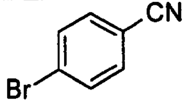
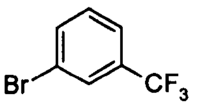
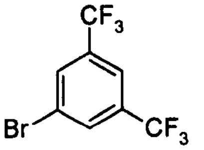
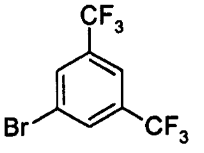
Aryl Halide		Activator	Catalyst	Product	Yield	Figure
	**2**	CsF	$Pd_2(dba)_3$/ PPh_3	**3**	1%	4.53
	**62**	TBAF	$Pd_2(dba)_3$/ P(2-furyl)$_3$	**68**	7%	4.63
	**69**	NaOH	$Pd(OAc)_2$/ PPh_3	**70**	36%	4.67
	**69**	KF	$Pd(OAc)_2$/ PPh_3	**70**	62%	4.68

Figure 4.83: Cross-coupling reactions with chlorogermanes

The conditions for the three reactions are similar, with perhaps the most significant differences being the nature of the catalyst and the number of equivalents of activator. It is noteworthy that 4-bromobenzonitrile failed to give a coupling reaction with trifurylphenylgermane **60**, suggesting that the choice of aryl halide may have had some effect on the poor coupling of the initial chlorogermane study. The two poor reactions also share a common palladium source, whereas the successful reaction utilises a pre-formed catalyst of palladium(II) acetate and triphenylphosphine, which is an effective source of a palladium(0) catalyst. It seems likely that this, in conjunction with the induction period allowing dichlorogermane **50** to react with fluoride and associated water, is the major factor behind the dramatic improvement in reactivity.

The current synthesis of dichlorogermanes **50** and **81** relies on selectively removing the electron rich tolyl or anisyl groups with electrophiles. In order to broaden the scope of the arylgermane coupling partner it is desirable to identify a more general synthetic approach. A modification of the dichloroanisylgermane chemistry developed in the group could solve this problem.

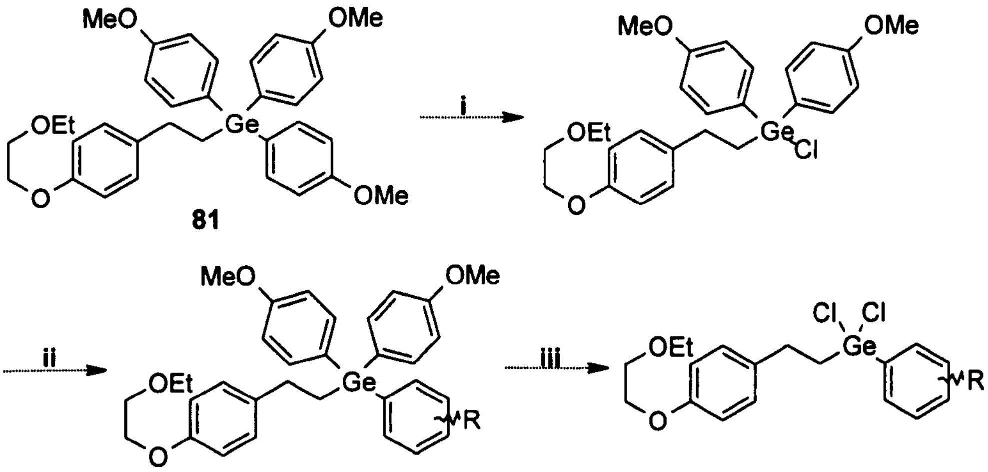


Figure 4.84: Potential synthesis of varied dichloroarylgermanes

Reagents and conditions: i) mild acid, selective for mono-dearylation, ii) aryl metal, iii) stronger acid, selective for di-dearylation.

Such an approach is contingent on the aryl group for cross-coupling being less electron rich than *p*-anisyl groups, and also being stable to acid. Other electron rich aryls that could be utilised in place of *p*-anisyl include 2-furyl and 2-thienyl.

4.4.2 Relative cross-coupling reactivity of chlorogermanes and chlorosilanes

In general, the susceptibility of group 14 metals towards hypervalency increases as the periodic table is descended. From the position of germanium within group 14 of the periodic table it might be expected, *a priori*, that organogermanes would display a susceptibility to hypervalency intermediate between that of organosilanes and organostannanes. Drawing on the mechanistic situation outlined for organosilanes (*vide supra*), this might be expected to translate into an intermediate susceptibility towards transmetallation and cross-coupling.

It is clear from the comparison between the reactivity of Vedejs' carbastannatranes and Kosugi's carbagermatranes, discussed in sections 1.2.2 and 1.5.1 respectively, that organostannanes are significantly more reactive towards cross-coupling than organogermanes. On the evidence of publications to date it is not, however, possible to reliably quantify the relative susceptibilities towards cross-coupling of organogermanes and organosilanes as comparative studies have not been published. The work in this thesis enables some of the first direct comparisons to be drawn between silicon and germanium.

One of the most striking features of this work was the difference between the reactivity of dichlorotolylgermane **50** and Hiyama's dichloroethyltolylsilane[54] in the palladium catalysed, hydroxide mediated coupling with 3,5-bistrifluoromethylbromobenzene.

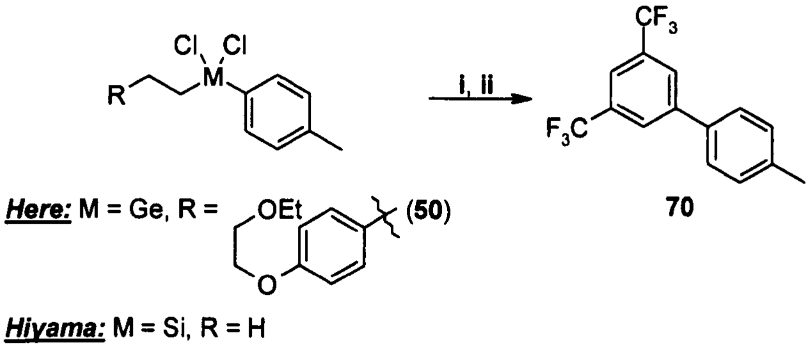


Figure 4.85: Hydroxide mediated cross-coupling of dichloroethyltolylsilane and dichlorogermane 50

Reagents and conditions: i) NaOH (6eq), THF, rt, 3h; ii) 3,5-bistrifluoromethylbromobenzene, Pd(OAc)$_2$ (1mol%), PPh$_3$ (2mol%), 60°C, 39h.

Whilst it was pleasing to identify successful cross-coupling conditions for organogermanes, it was surprising to see that the yield for dichlorogermane **50** was markedly inferior to the yield for dichloroethyltolylsilane (36% for Ge, *cf.* 85% for Si[54]). Contrary to the original hypothesis that organogermanes would be *intermediate* between organostannanes and organosilanes, the reactivity instead appears to follow the trend Si > Ge << Sn.

This surprising order of reactivity may be explained by considering the scandide, or transition metal, contraction, which describes the effect on the atomic properties of p-block elements resulting from filling the d-orbitals of period 4 for the first time.[200] Although the effect is felt for all p-block elements in periods 4, 5 and 6, it is strongest for the post-scandide elements in period 4, which are the first in the periodic table to be affected by a full d-orbital.

Electrons in d-orbitals are poorly shielding, meaning that the effect of the increased nuclear charge as period 4 is traversed is felt more strongly on the valence electrons of period 4 p-block elements than would be expected. The most obvious illustration of this is the smaller than expected covalent radii for germanium as a result of the scandide contraction, and for lead due to the lanthanide contraction resulting from the filled 4f-orbital.

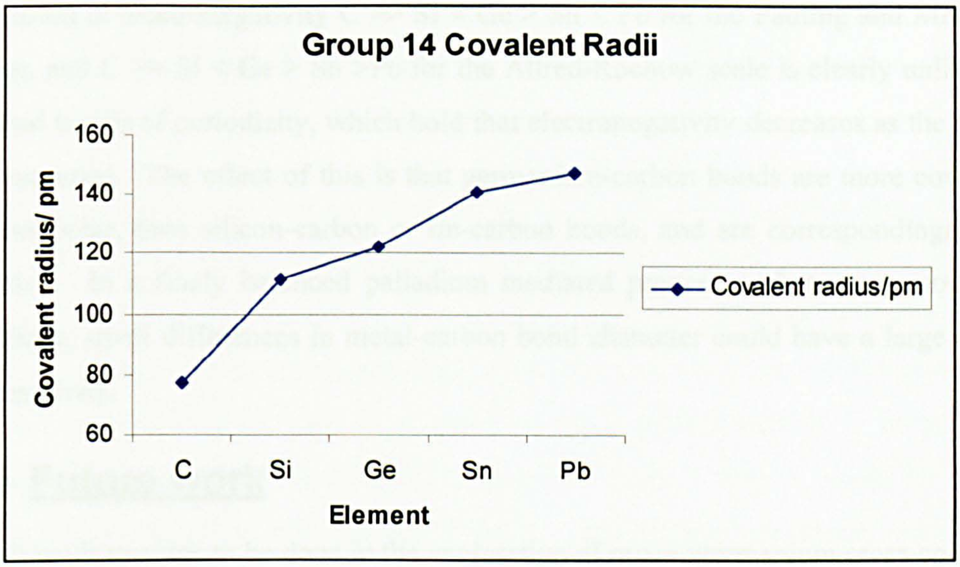


Figure 4.86: Covalent radii of group 14 elements[201]

The scandide and lanthanide contractions also affect the electronegativities of the group 14 elements, and consequently affect the chemistry of silicon, germanium, tin and lead, to the extent that germanium has more in common with carbon than silicon or tin, and silicon has more in common with tin, than with carbon or germanium.

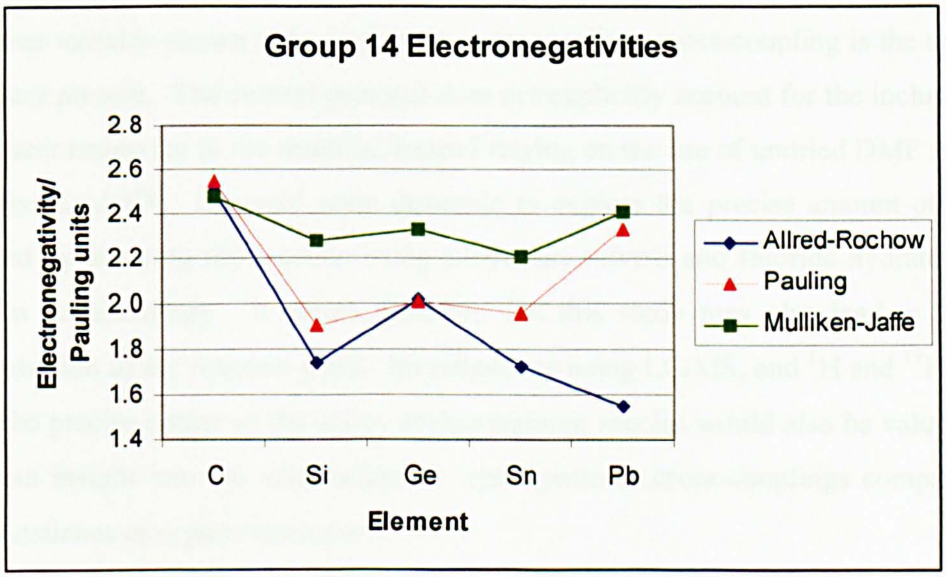


Figure 4.87: Electronegativities of group 14 elements[201]

The trend in electronegativity C >> Si < Ge > Sn < Pb for the Pauling and Mulliken scales, and C >> Si < Ge > Sn >Pb for the Allred-Rochow scale is clearly unlike the general trends of periodicity, which hold that electronegativity decreases as the group is descended. The effect of this is that germanium-carbon bonds are more covalent, or less polar, than silicon-carbon or tin-carbon bonds, and are correspondingly less reactive. In a finely balanced palladium mediated process such as cross-coupling reactions, small differences in metal-carbon bond character could have a large effect on reactivity.

4.5 Future work

Much work remains to be done in the exploration of organogermanium cross-coupling chemistry.

The current catalytic system appears unable to facilitate the coupling of electron rich aryl halides. Although they are routinely less reactive than electron deficient aryl halides it is nevertheless rare for electron rich aryls to be wholly unreactive and it would be desirable if a more efficient catalytic system could be identified to overcome this limitation of the scope of reactivity.

Another variable shown to be important in organosilane cross-coupling is the amount of water present. The current protocol does not explicitly account for the inclusion of the water necessary to the reaction, instead relying on the use of undried DMF solvent and hydrated KF. It would seem desirable to explore the precise amount of water needed by studying the reaction using anhydrous solvent and fluoride hydrates with known stoichiometry. It seems plausible that this study may also lead to further optimisation of the reaction yield. Investigations using LC/MS, and ^{1}H and ^{19}F NMR into the precise nature of the active arylgermanium species would also be valuable to gain an insight into the mechanism of organogermane cross-couplings compared to organosilanes or organostannanes.

Another area of study that appears important will be investigations of the synthesis and reactivity of germanols. It is known that germoxane oligomers are formed in preference to germadiols and germatriols, but the synthesis of a mono germanol may be possible. The reactivity of such a compound could then be investigated in light of the proposed mechanistic pathways for silanol couplings that allow the pre-coordination of the organometallic with the palladium catalyst.

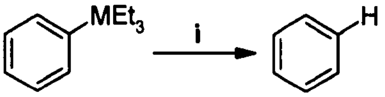
Chlorogermanes are interesting from the point of view of expanding the scope of group 14 organometallic cross-coupling chemistry and gaining an insight into the relative reactivity of the group 14 elements, and the differences between the chemistries of silicon germanium and tin. However, they remain a reactive and labile species, and would be unlikely to provide a practical applied solution to the problem of solid phase organogermane cross-coupling. In light of this, it would be highly desirable to develop a practical safety-catch organogermanium linker. The brief initial investigation of germyl hydrides as cross-coupling partners has been unsuccessful, but these compounds remain as a potential coupling partner if an effective method for hydrolysing the germanium-hydrogen bond can be identified.

Once an appropriate safety catch linker has been developed then it remains to transfer this chemistry to the solid phase and apply it to the synthesis of diverse libraries of *e.g.* pharmaceutical compounds with a biaryl motif. Another area of study within the research group where this work could have direct relevance is in the cleavage of semi-conducting oligothiophenes from germanium. The electronic properties of oligothiophenes are affected by the nature of the end groups, and various aromatic molecules have been used in this regard.

5 Friedel-Crafts degermylation results and discussion

5.1 Acetyldegermylation of aryltrimethylgermanes

The second area of arylgermane chemistry explored in this project was Friedel-Crafts acyldegermylation, using an acylium ion as the electrophile to form aryl ketones. This methodology represents another opportunity to cleave library molecules from a germanium based linker with a carbon-based electrophile, and, as described in chapter 2, there is literature precedent for the analogous *ipso* demetallation of arylsilanes and arylstannanes. The reactivity of Group 14 aryl-metal species towards electrophiles is known to be related to the magnitude of their β-effect, which increases in the order Si < Ge << Sn, as demonstrated by Eaborn's 1960 study of the relative rate of cleavage of aryl-metal bonds by proton electrophiles.[13]



Reagents and conditions: i) $HClO_4$, solvent, H_2O

M	Solvent	K_{rel}
Si	MeOH	1
Ge	MeOH	36
Sn	EtOH	3.5×10^5
Pb	EtOH	2×10^8

Figure 5.1: Relative magnitude of the β-effect for group 14 metals

Interpolation of the chemistry of silicon and tin thus led to a high degree of confidence that the reaction could also be applied to arylgermanes.

The starting point for this work was to identify conditions that could be applied to germanium. Eaborn's initial work had used aluminium(III) chloride in carbon disulfide as the solvent,[153] but later work from other groups had shown that CH_2Cl_2 could also be used as solvent.[156,159] This seemed to be a better starting point, and it was decided to replicate Dunogues' acyldesilylation of 3,5-xylene,[202] using a modified method taken from Dunogues' 1993 refined acyldesilylation method[150] and Katz' 1993 acyldesilylation of naphthalenes and acenaphthylenes.[161]

Dunogues synthesised silyl xylene **94** from *m*-xylene, starting with a "silicon Birch" reduction to give the unconjugated 1,5-dimethyl-3,6-disilyl-1,4-cyclohexadiene, which was aromatised with *p*-chloranil to gave a mixture of the disilyl and 5-silyl *m*-xylenes, which were separated by distillation to give silyl xylene **94** in 60-64% yield. We anticipated that lithiation of bromoxylene **77** using n-BuLi, followed by quenching with TMS-Cl would also furnish the desired compound.

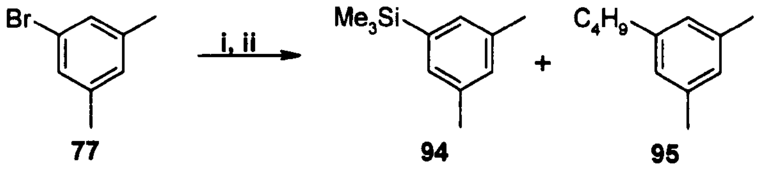
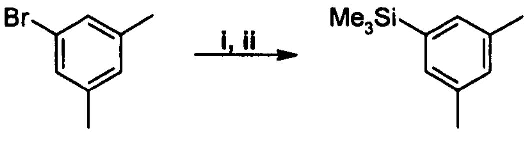


Figure 5.2: Attempted silylation of 3,5-bromoxylene

Reagents and conditions: i) n-BuLi, THF -78°C, 30min; ii) TMS-Cl, -78°C → rt, 17h.

Although the reaction mixture appeared as a single spot by TLC, analysis of the reaction mixture by GC/MS and ^{1}H NMR revealed a mixture of the desired silyl xylene **94**, and butyl xylene **95**, presumably as a result of the reaction of excess aryl lithium with the butyl bromide by-product. In order to address this issue, the reaction was repeated using s-BuLi and t-BuLi, and instead of warming to rt overnight was stirred at -78°C for 30 min before being warmed to rt over just 1 hour after the silyl chloride had been added.



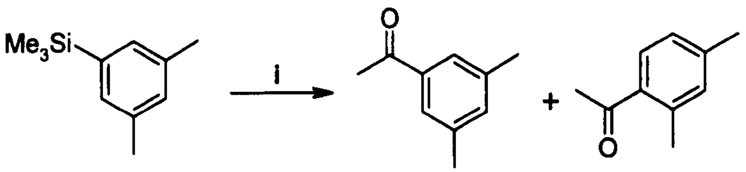
77 94

Reagents and conditions: i) alkyl lithium, THF -78°C, 30min; ii) t-BuLi, THF -78°C, 30min; iii) TMS-Cl, -78°C 30min, → rt, 1h.

Alkyl lithium	Yield
s-BuLi	68%
t-BuLi	36%

Figure 5.3: Silylation of 3,5-bromoxylene with alternate alkyl lithiums

In each case a pure sample of silyl xylene **94** was obtained. Owing to the superior yield, s-BuLi was employed in further experiments.



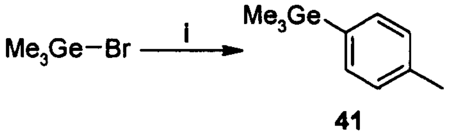
94 96 97

Figure 5.4: Acylation of silyl xylene 94

Reagents and conditions: i) aluminium(III) chloride, AcCl, CH_2Cl_2, 0°C → -78°C 30min; ii) **94**, CH_2Cl_2, -78°C 1h, 96%.

The desired *ipso* acyldesilylated product **96** was not the sole compound isolated; ^{1}H NMR and GC/MS indicated that the *ortho* acyldesilylated isomer **97** had also been formed, giving a yield of 96% for the two isomers. Analysis of the ^{1}H NMR integrals indicated that the two isomers were present in a *ca.* 50/50 ratio. This is in contrast to Dunogues' claim that the reaction is regiospecific.

It was decided to use trimethylgermyl substituted aromatics in order to determine the scope of reactivity of arylgermanes towards acyldegermylation. Tolylgermane **41** was synthesised *via* reaction of trimethylgermyl bromide with commercial *p*-tolylmagnesium bromide.



41

Figure 5.5: Synthesis of trimethyltolylgermane

Reagents and conditions: i) *p*-TolMgBr, THF, rt, 4.5h, 91%.

Other arylgermanes were synthesised *via* lithiation of the appropriate aryl bromide, followed by quenching with trimethylgermanium bromide (TMG-Br).

Reagents and conditions: i) s-BuLi, THF -78°C; ii) TMG-Br, -78°C, → rt.

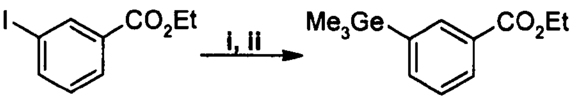
Entry	Aryl bromide		Lithiation time	Time at -78°C	Time at rt	Product	Yield
1	*p*-Methoxy	**12**	15min(a)	15min	15min	**101**	89%
2	*m*-Methoxy	**98**	30min(a)	30min	30min	**102**	20%
3	*o*-Methyl	**99**	15min(a)	15min	15min	**103**	72%
4	*m*-Methyl	**100**	30min(a)	30min	15min	**104**	-
5	3,5-Dimethyl	**77**	30min(a)	30min	15min	**105**	-
6	*m*-Methyl	**100**	30min(b)	30min	15min	**104**	12%(c)
7	3,5-Dimethyl	**77**	30min(b)	30min	15min	**105**	69%(d)
8	2,6-Dimethyl	**106**	45min(b)	45min	30min	**107**	80%
9	*o*-Pyridyl	**76**	45min(b)	30min	30min	**108**	81%

(a): s-BuLi was used (b): n-BuLi was used (c): The starting material was the crude product from entry 4. Yield is calculated from the amount of aryl bromide used in entry 4 (d): The starting material was the crude product from entry 5. Yield is calculated from the amount of aryl bromide used in entry 5

Figure 5.6: Germylation of aryl bromides

There was incomplete metallation in the reactions with 3-bromotoluene **100**, and *meta* bromoxylene 77 using s-BuLi (entries 4 and 5), and in each case, a mixture of desired product germane and starting material bromide was obtained. The crude reaction mixtures were further exposed to n-BuLi and TMG-Br to give samples of pure product (entries 6 and 7). *o*-Xylene **107** and pyridine **108** were also synthesised using n-BuLi (entries 8 and 9).

meta Benzoate **110** was prepared using Knochel's i-PrMgCl chemistry.[203]

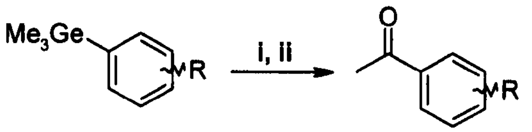


109 **110**

Figure 5.7: Germylation of aryl iodides using i-PrMgCl

Reagents and conditions: i) i-PrMgCl, THF -40°C, 90min; ii) TMG-Br, -40°C, 2h 40min, 75%.

With a range of arylgermanes in hand, attention turned to exploring the scope of *ipso* acyldegermylation. It was anticipated that, in accordance with the β-effect for group 14 metals, arylgermane bonds should be more reactive towards acylium ions than aryl silanes. Consequently, the method used for the *ipso*-acyldesilylation of silyl xylene **94** was employed.



Reagents and conditions: i) aluminium(III) chloride, AcCl, CH_2Cl_2, 0°C → -78°C 1h; ii) Arylgermane, CH_2Cl_2, -78°C 1h, → rt 1h.

Entry	Arylgermane		Product	Yield
1	*p*-Methyl	**41**	**111**	85%
2	*p*- Methoxy	**101**	**112**	63%
3	*m*-Methoxy	**102**	**113**	78% (a)
4	*o*-Methyl	**103**	-	- (b)
5	*m*-Methyl	**104**	**114**	65%
6	3,5-Dimethyl	**105**	**96 + 97**	76% (c)
7	2,6-Dimethyl	**107**	**115**	53%
8	*o*-Pyridyl	**108**	-	-
9	*m*-Ethyl benzoate	**110**	-	-

(a) Acylation was directed by the methoxy group; degermylation was not observed (b) No identifiable compounds isolated (c) Mixture of 3,5 and 2,4 dimethyl acetophenone isomers isolated

Figure 5.8: Acylation of arylgermanes

The results for the *ipso* acyldegermylation revealed some interesting facets of the strength of germanium's β effect and its ability to direct *ipso* substitution. *p*-Tolylgermane **41** (entry 1), *p*-anisylgermane **101** (entry 2), *m*-tolylgermane **104** (entry 5), and 2,6-xylene **107** (entry 7) gave the expected *ipso* substituted acetophenones in good yield. The successful reaction of the sterically hindered 2,6-xylene **107** can be ascribed to the release of steric crowding when the Wheland intermediate is formed.[204] Surprisingly *o*-methyl arylgermane **103** (entry 4) did not give any identifiable products, in contrast to Sasaki's report of a 45% yield of the *ipso* substituted acetophenone when *o*-methyl aryl silane was exposed to $TiCl_4$/AcCl.[156] This observation could perhaps be ascribed to preferential protodegermylation if any moisture was present in the reaction media. Similarly to silyl xylene **94**, 3,5-dimethyl arylgermane **105** (entry 6) gave a *ca.* 50/50 mixture of 3,5 dimethyl and 2,4-dimethyl acetophenones **96** and **97** in 76% combined yield.

Electron deficient pyridylgermane **108** and germyl benzoate **110** (entries 8 and 9 respectively) both failed to undergo degermylation at -78°C, rt, or even in refluxing CH_2Cl_2. It is possible that the unreactivity of pyridylgermane **108** could also be attributed to coordination of the pyridine nitrogen to any of the Lewis acids present.

One of the more interesting results was the reaction of *m*-anisylgermane **102** with acetyl chloride. Dunogues has reported for silicon that acylation is preferentially influenced by strong *ortho*/*para* directing substituents.[205]

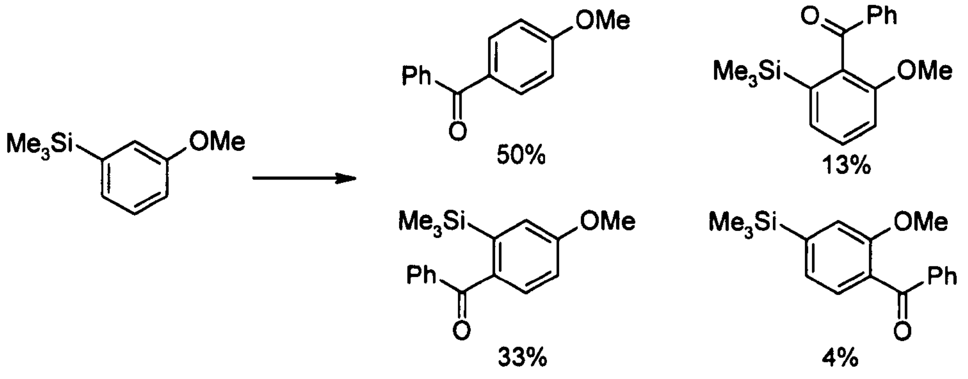
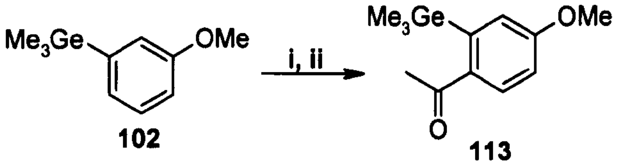


Figure 5.9: Dunogues' acylation of *m*-anisylsilane

Reagents and conditions: i) aluminium(III) chloride, PhCOCl, CS_2, 0°C.

We had hoped that the *ipso* directing effect of a germanium substituent would be sufficient to overcome the *ortho*/*para* directing effect of the methoxy substituent.



102

113

Figure 5.10: Acylation of arylgermanes

Reagents and conditions: i) aluminium(III) chloride, AcCl, CH_2Cl_2, 0°C → -78°C 1h; ii) arylgermane, CH_2Cl_2, -78°C 1h, → rt 1h, 78%.

In the event, we found that the methoxy group still preferentially directed the acylation, to give the trisubstituted arylgermane **113**. Acylation *para* to the methoxy group and *ortho* to the germyl substituents, rather than *ortho* to the methoxy group and *para* to germanium was confirmed by a nuclear Overhauser effect experiment (see experimental). In light of the fact that both $SiMe_3$ and $GeMe_3$ substituents have similar Hammett σ^+ values (-0.14 and –0.19 respectively),[206] which are much less negative than that for OMe (–0.78),[207] perhaps this selectivity is not surprising. Arylgermane **82** was further subjected to aluminium(III) chloride/AcCl to see if a second acyl group could be installed by *ipso* degermylation, but no identifiable products could be recovered.

Finally, to exemplify the Friedel-Crafts acyldegermylation of aromatic groups from our linker model system, dimethylanisylgermane **13** was exposed to aluminium(III) chloride/AcCl, giving 4-methoxy acetophenone **112** in 52% yield.

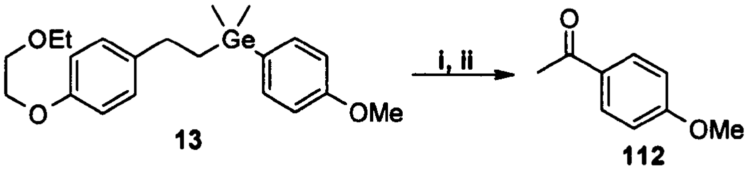


Figure 5.11: Acylation of arylgermanes

Reagents and conditions: i) aluminium(III) chloride, AcCl, CH_2Cl_2, 0°C → -78°C 1h; ii) arylgermane, CH_2Cl_2, -78°C 1h, → rt 1h, 52%.

5.2 Conclusions

In light of the scant literature precedent, this work represents the first properly reported study of acyldegermylation and has allowed some conclusions to be drawn about the susceptibility of arylgermanes towards *ipso* demetallative cleavage with acylium ions to form aryl ketones. There are some limitations on the nature of the aryl group at germanium; the most appropriate aryl groups are those that are electron neutral or slightly electron rich. Aromatic rings with strong electron donating substituents can find their Friedel-Crafts chemistry directed not by the germanium substituent, but by the electron donating group instead. This was disappointing, as it had been hoped that the *ipso* directing effect of germanium would prove to be stronger than the *ortho/para* directing effects of *e.g.* methoxy substituents.

It had also been hoped that the increased reactivity of C-Ge bonds towards electrophiles in comparison to C-H bonds (and also C-Si bonds)[13] might have facilitated acylation of strongly electron deficient rings, which are normally unreactive towards this form of chemistry. However, this does not appear to be the case, as both pyridine **109** and *meta*-benzoate **110** remained unchanged by the action of aluminium(III) chloride/AcCl.

The effect of steric hindrance remains ambiguous; whilst the highly congested 2,6-xylene **107** reacted cleanly, *ortho*-toluene **103** did not. It is unclear whether the failure of *ortho*-toluene **103** to give the desired product is related to the substitution pattern or not, as the reactivity of xylene **107** could be ascribed to a release of the strain resulting from steric crowding, and may be an atypical case.

It had been hoped at the outset that the germanium *ipso* directing influence would be sufficiently enhanced relative to that of silicon to allow for the regioselective synthesis of arylketones that are otherwise difficult to construct. The results obtained suggest that this is not the case, and that the Friedel-Crafts chemistry of arylgermanes is similar to that of arylsilanes. Perhaps this is unsurprising as the magnitude of the β-effect on going from silicon to germanium is only increased by a factor of 36 (*vide supra*). Nevertheless, this methodology still represents a powerful opportunity for the diversification of aromatic libraries containing aromatic ketones.

5.3 Future work

The work described above is only a preliminary study of Friedel-Crafts acyldemetallation, and there is a need for further investigation in this area.

Firstly, this work has delineated the scope of the arylgermane undergoing acylation, but has not looked at the nature of the acylating agent. It would be valuable to investigate the reactivity of aromatic acyl chlorides with varying electronic characteristics, a range of aliphatic acyl chlorides, including some with substitution at the α-position and also of sulfonyl chlorides. In addition, it still remains to be shown that this chemistry can be carried out on the solid phase.

Once the scope of the acylating agents has been established then one potential application of this methodology is the synthesis of libraries of pharmaceutical compounds that contain an aryl ketone moiety. This chemistry may also find significant use in another project within the group in the solid phase synthesis of semi-conducting oligothiophenes as a means of installing end-groups (*vide supra*), typically these end groups may be long chain alkyls. In practice, these alkyl groups are often installed as ketones due to the fact that Friedel-Crafts acylation is generally superior to Friedel-Crafts alkylation and because the polar carbonyl group facilitates purification by chromatography. Thus, following purification the ketone carbonyl functional group can be cleanly reduced to a methylene unit using Lewis acid promoted hydride reduction.

6 Experimental

6.1 General directions

Solvents and reagents: See appendix 8.1 for preparation of solvents, and appendix 8.2 for the preparation of reagents.

Chromatography: Flash chromatography was carried out on Silica gel (BDH Silica gel for flash chromatography) according to the method described by Still,[208] or by using either Isolute Flash Silica (1g, 5g, 50g) or Varian Bond Elut Si (10g) SPE cartridges in conjunction with a Varian Vac-Elut-20 vacuum manifold. TLC was performed on aluminium backed silica gel plates (Merck Silica gel 60 F_{254}) which were developed with UV fluorescence (254 nm and 365nm) and $KMnO_4$(aq)/Δ.

^1H NMR spectra: These were recorded at 250MHz on Bruker AC-250 instrument or at 400MHz on a Bruker AM-400 instrument. Chemical shifts (δ_H) are given in parts per million (ppm) as referenced to the appropriate residual solvent peak. Broad signals are assigned as b. All spectra were compared with reference spectra of authentic products and reagents.

^{13}C NMR spectra: These were recorded at 63MHz on Bruker AC-250 instrument or at 101MHz on a Bruker AM-400 instrument. Chemical shifts (δ_C) are given in parts per million (ppm) as referenced to $CHCl_3$, and are assigned as s, d, t, and q, for C, CH, CH_2, and CH_3 respectively.

Mass Spectra: Low resolution and high-resolution spectra were recorded on a VG Prospec spectrometer, with molecular ions and major peaks being reported. Intensities are given as percentages of the base peak. Molecular weights are calculated using ^{74}Ge, ^{35}Cl and ^{79}Br isotopes. HRMS values are valid to ±5ppm.

GC/MS: Analyses were carried out using a Perkin Elmer Turbomass mass spectrometer and Autosystem XL gas chromatograph. GC methods are outlined in appendix 7.3 and retention times are given in minutes. MS data is reported as above and all EI spectra were compared to the NIST database to confirm identity.

LC/MS: Analyses were carried out using a Micromass LCZ mass spectrometer and Hewlett Packard 1100 liquid chromatograph. LC methods are outlined in appendix 7.4 and retention times are given in minutes. MS data is reported as above.

Elemental analysis: Analyses were carried out by Mr Alan Jones (University of Sheffield) using a Perkin Elmer 2400 CHN elemental analyser.

Melting points: Analyses were carried out using a Khofler hot stage or Gallenkamp melting point apparatus and are uncorrected.

Microwave: Reactions using microwave irradiation were carried out using a Personal Chemistry Emrys™ creator.

6.2 Cross-coupling

6.2.1 Approaches towards dimethylarylgermane cross-coupling

6.2.1.1 Synthesis of reaction materials

Dichlorogermylidene 1,4-dioxane complex (7)

$GeCl_2 \cdot C_4H_8O_2$
7

Molecular Weight =231.60
Molecular Formula =$C_4H_8Cl_2GeO_2$

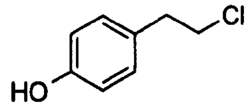
Method 1[209,210]

According to the method of Mironov,[209,210] tetramethyldisiloxane (0.593g, 4.41mmol), germanium(IV) chloride **6** (0.940g, 4.38mmol), and 1,4-dioxane (2mL) were refluxed at 100°C for 3h. After cooling to 0°C the suspended white needle crystals were isolated by filtration, and then washed with cold chloroform (3 x 30mL). Drying under high vacuum gave dichlorogermylidene 7 as white needles (0.761g, 3.29mmol, 75%). **R*f*** 0.00 (CH_2Cl_2); **Mp** 178-182°C (decomp.) (*cf.* 178-180°C[209,210]); **MS** (EI) *m/z* 144 ($M^{\cdot+}$ 57%), 109 (83%), 88 (100%), 74 (14%), 58 (80%).

Method 2[190]

According to the method of Kouvetakis,[190] to a suspension of lithium aluminium hydride (0.025g, 0.669mmol) in anhydrous toluene (25mL) under N_2, was added triethylsilane (5.6mL, 4.07g, 35.1mmol), anhydrous 1,4-dioxane (10.2mL, 10.5g, 0.119mol) and germanium(IV) chloride **6** (2.00mL, 3.76g, 17.5mmol). The mixture was then heated at 84°C for 14 hours. No colour change was observed, so the temperature was increased to 100°C for 5 hours. Still no colour change was observed so the mixture was heated at 84°C for 17 hours, after which the temperature was increased to 120°C. After 2.5 hours at the elevated temperature a rapid colour change was observed from clear and colourless to orange. Heating was stopped immediately, the solution filtered whilst still hot, and the resulting solid further washed with hot toluene. The filtrate was then cooled to -20°C, filtered and the crystals washed with cold 1,4-dioxane to give dichlorogermylidene complex **7** as cream needles (0.708g, 3.06mmol, 17%). Analytical data as above.

4-(2-Chloroethyl)phenol (5)[211]



5

Molecular Weight =156.61
Molecular Formula =C_8H_9ClO

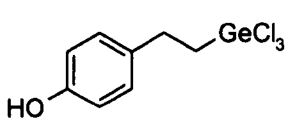
Method 1: Sealed tube

4-(2-Hydroxyethyl)phenol **4** (0.498g, 3.60mmol) and c.HCl (3mL, 30.0mmol) were heated in a sealed tube at 103°C for 3h. After cooling, the reaction mixture was diluted with H_2O (30mL), and then extracted with Et_2O (3 × 30mL). Organic extracts were combined, dried with $MgSO_4$ and concentrated *in vacuo* to give a brown oil. Purification by column chromatography (10 × 2.5cm Silica gel eluted with CH_2Cl_2) gave chlorophenol **5** as a pale brown oil that formed white fibres on standing: (0.505g, 3.22mmol, 90%). **R*f*** 0.31 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$) δ 2.99 (2H, t, *J* 7.0, CH_2CH_2Cl), 3.67 (2H, t, *J* 7.0, CH_2CH_2Cl), 4.89 (1H, s, O*H*), 6.78 (2H, d, *J* 9.0, HOCC*H*CHCCH$_2$), 7.09 (2H, d, *J* 9.0, HOCCHC*H*CCH$_2$); **MS** (EI) *m/z* 156 (M^{+} 16%), 107 (100%), 91 (8%), 77 (15%).

Method 2: Microwave

4-(2-Hydroxyethyl)phenol **4** (0.508g, 3.68mmol) and concentrated aqueous HCl (2mL) were combined in a microwave reaction tube, sealed and irradiated at 165°C for 180 seconds with a fixed hold time. The reaction mixture was extracted with CH_2Cl_2 (2 × 10mL), filtered through a hydrophobic frit and concentrated *in vacuo*. The residue was purified with a 5g Silica gel SPE cartridge eluting with cyclohexane/EtOAc, 1/1 to give chlorophenol **5** as a clear colourless oil, which formed white fibres on standing (0.548g, 3.50mmol, 95%). Analytical data as above.

4-(2-Trichlorogermanylethyl)phenol (8)[175]



8

Molecular Weight =300.11
Molecular Formula =$C_8H_9Cl_3GeO$

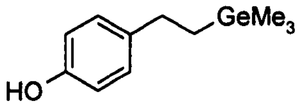
Method 1: Sealed tube

Chlorophenol **5** (0.467g, 2.98mmol) and dichlorogermylidene complex **7** (0.544g, 2.35mmol) were heated in a sealed tube at 140°C for 16h. After cooling, the mixture was diluted with CH_2Cl_2 (50mL), and added slowly and dropwise to H_2O (75mL) to give a white precipitate that was collected by filtration. The precipitate was washed with H_2O (3 × 60mL) and CH_2Cl_2 (3 × 60mL) and air-dried. The dry precipitate was dissolved in c.HCl (37% w/v, 50mL) and extracted with CH_2Cl_2 (3 × 75mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give trichlorogermylphenol **8** as a pale brown oil (0.520g, 1.73mmol, 74%). **R_f** 0.00 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$) δ 2.30 (2H, m, $CH_2C\mathit{H}_2GeCl_3$), 2.97 (2H, m, $C\mathit{H}_2CH_2GeCl_3$), 5.09 (1H, bs, O*H*), 6.79 (2H, d, *J* 9.0, HOCC*H*CHCCH$_2$), 7.10 (2H, d, *J* 9.0, HOCCHC*H*CCH$_2$); **MS** (EI) *m/z* 300 (M^{+} 9%), 179 (5%), 121 (85%), 107 (100%), 91 (24%), 77 (21%), 65 (15%).

Method 2: Microwave

Chlorophenol **5** (0.620g, 3.95mmol), and dichlorogermylidene complex **7** (0.855g, 3.69mmol) were irradiated in a microwave reaction tube at 140°C for 4 minutes with a fixed hold time. After cooling, the mixture was diluted with CH_2Cl_2 (25mL), and added slowly and dropwise to H_2O (60mL) to give a white precipitate that was collected by filtration. The precipitate was washed with H_2O (3 × 30mL) and CH_2Cl_2 (3 × 30mL) and air-dried. The dry precipitate was dissolved in c.HCl (50mL) and extracted with CH_2Cl_2 (3 × 25mL). The organic extracts were filtered through a hydrophobic frit and concentrated *in vacuo* to give trichlorogermylphenol **8** as a pale brown oil (0.798g, 2.66mmol, 72%). Analytical data as above.

4-(2-Trimethylgermanylethyl)phenol (9)[175]

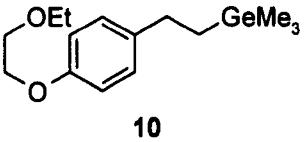


9

Molecular Weight =238.86
Molecular Formula =$C_{11}H_{18}GeO$

A solution of MeMgBr (32.0mL, 3.0M in Et_2O, 96.0mmol) was added by cannula to trichlorogermylphenol **8** (4.78g, 16.0mmol) in toluene (20mL). The resulting mixture was heated at 110°C for 16h, the reaction was then quenched with H_2O (10mL). HCl (1M, 100mL) was added to dissolve precipitates, and was then extracted with Et_2O (3 × 100mL). The organic washings were dried with $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (15 × 5cm Silica gel, eluted petrol/EtOAc, 9/1) gave trimethylgermylphenol **9** as a brown oil (2.91g, 12.2mmol, 76%). **R_f** 0.36 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 0.00 (9H, s, Ge(C*H*$_3$)$_3$), 0.95, (2H, m, CH_2C*H*$_2$Ge(CH_3)$_3$), 2.51 (2H, m, C*H*$_2$$CH_2$Ge($CH_3$)$_3$), 5.25, (1H, s, OH), 6.63, (2H, d, *J* 8.5, HOCC*H*CHCCH_2), 7.00, (2H, d, *J* 8.5, HOCCHC*H*CCH_2); **MS** (EI) *m/z* 240 ($M^{\cdot+}$ 8%), 225 (65%), 197 (18%), 119 (100%), 105 (82%), 77 (33%).

4-[(2-Trimethylgermanyl)ethyl]phenyl (2-ethoxyethyl) ether (10)[175]



10

Molecular Weight =310.96
Molecular Formula =$C_{15}H_{26}GeO_2$

Method 1: TBAI catalyst

Trimethylgermylphenol **9** (0.507g, 2.12mmol), cesium carbonate (0.826g, 2.54mmol) and tetrabutylammonium iodide (0.0788g, 0.218mmol) were dissolved in 20mL

MeCN under N_2 atmosphere. To this resulting solution was added 2-chloroethyl ethyl ether (0.460g, 0.47mL, 4.24mmol). The solution was then heated at reflux for 24 hours, until no phenol remained by TLC. Purification by column chromatography (7cm silica gel eluting with petrol/EtOAc, 9/1) gave trimethylgermyl ether **10** as a light brown oil (0.605g, 1.95mmol, 92%). **R_f** 0.73 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 0.0 (9H, s, Ge(C*H*$_3$)$_3$), 0.92 (2H, m, CH_2C*H*$_2$Ge(CH_3)$_3$), 1.14 (3H, t, *J* 7.0, C*H*$_3$$CH_2$O), 2.52 (2H, m C*H*$_2$$CH_2$Ge($CH_3$)$_3$), 3.50 (2H, q, *J* 7.0, CH_3C*H*$_2$O), 3.68 (2H, t, *J* 5.0, OC*H*$_2$$CH_2$OAr), 4.00 (2H, t, *J* 5.0, OCH_2C*H*$_2$OAr), 6.74 (2H, d, *J* 8.5, OCC*H*CHCCH$_2$), 7.00 (2H, d, *J* 8.5, OCCHC*H*CCH$_2$); **MS** (EI) *m/z* 312 (M^+ 6%), 297 (29%), 269 (5%), 223 (4%), 147 (18%), 119 (79%), 73 (100%).

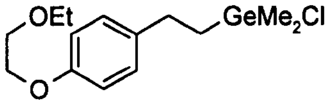
Method 2: Et_4NI catalyst

Trimethylgermylphenol **9** (0.247g, 1.03mmol), cesium carbonate (0.439g, 1.35mmol) and tetraethylammonium iodide (0.0287g, 0.112mmol) were dissolved in 4mL MeCN under N_2 atmosphere. To this resulting solution was added 2-chloroethyl ethyl ether (0.346g, 0.35mL, 3.19mmol). The solution was then heated at reflux for 16.5 hours, until no phenol remained by TLC. Purification by column chromatography (7 × 3cm silica gel eluting with petrol/EtOAc, 9/1) gave trimethylgermyl ether **10** as a light brown oil (0.309g, 0.993mmol, 96%). Analytical data as above.

Method 3: CsI catalyst

Trimethylgermylphenol **9** (0.259g, 1.08mmol), cesium carbonate (0.446g, 1.37mmol) and cesium iodide (0.0300g, 0.115mmol) were dissolved in 4mL MeCN under N_2 atmosphere. To this resulting solution was added 2-chloroethyl ethyl ether (0.346g, 0.35mL, 3.19mmol). The solution was then heated at reflux for 24 hours, until no phenol remained by TLC. Purification by column chromatography (7 × 3cm silica gel eluting with petrol/EtOAc, 9/1) gave trimethylgermyl ether **10** as a light brown oil (0.296g, 0.950mmol, 88%). Analytical data as above.

4-{[2-Chlorodimethylgermanyl]ethyl}phenyl (2-ethoxyethyl) ether (11)[175]

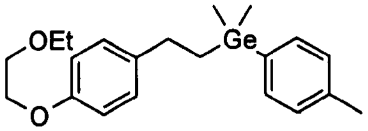


11

Molecular Weight =331.38
Molecular Formula =$C_{14}H_{23}ClGeO_2$

Trimethylgermyl ether **10** (0.605g, 1.95mmol) was dissolved in anhydrous $MeNO_2$. $SnCl_4$ (2.54g, 1.14mL, 9.75mmol) was then added by syringe and the solution heated at 50°C overnight, TLC indicated that no trimethylgermane ether **10** remained. The sample was then purified by distillation at 80°C under a high vacuum (0.5mmHg) for 3 hours. ^1H NMR indicated that neither $MeSnCl_3$ by-product or trimethylgermane ether **10** starting material were present, giving chlorodimethylgermane **11** as a dark brown liquid (0.644g, 1.95mmol, 100%). **R*f*** 0.00 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 0.59 (6H, s, $Ge(CH_3)_2Cl$), 0.92 (2H, m, $CH_2C\mathit{H}_2Ge(CH_3)_2Cl$), 1.14 (3H, t, *J* 7.0, CH_3CH_2O), 2.52 (2H, m, $C\mathit{H}_2CH_2Ge(CH_3)_2Cl$), 3.50 (2H, q, *J* 7.0, $CH_3C\mathit{H}_2O$), 3.68 (2H, t, *J* 5.0, $OC\mathit{H}_2CH_2OAr$), 4.00 (2H, t, *J* 5.0, $OCH_2C\mathit{H}_2OAr$), 6.74 (2H, d, *J* 8.5, $OCC\mathit{H}CHCCH_2$), 7.00 (2H, d, *J* 8.5, $OCCHC\mathit{H}CCH_2$); **MS** (EI) *m/z* 332 (M^+ 57%), 297 (6%), 281 (7%), 224 (14%), 193 (14%), 139 (27%), 121 (32%), 73 (76%), 45 (100%).

4-{[2-dimethyl-(4-methylphenyl)germanyl]ethyl}phenyl (2-ethoxyethyl) ether (1)

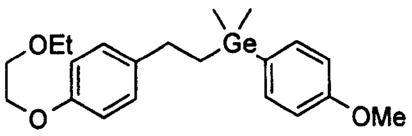


1

Molecular Weight =387.06
Molecular Formula =$C_{21}H_{30}GeO_2$

Chlorodimethylgermane **11** (0.553g, 1.67mmol) was placed in an N_2 atmosphere and dissolved in 10mL anhydrous toluene immediately after purification. A solution of *p*-TolMgBr in Et_2O (6.30mL, 6.30mmol, 1.0M) was added *via* syringe with stirring. The solution was then heated at reflux for 14 hours. Distilled H_2O (20mL) was added dropwise to destroy remaining *p*-TolMgBr, forming a white precipitate. 1M HCl (75mL) was added to dissolve precipitates; Et_2O (100mL) was added to dissolve organic components. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 75mL). Organic washings were combined, dried with $MgSO_4$, and evaporated. The resulting mixture was purified by column chromatography (7 × 18cm Silica gel eluted with CH_2Cl_2/toluene, 8/2) to give tolylgermane **1** as a dark brown oil (0.493g, 1.27mmol, 76%). **R_f** 0.42 (CH_2Cl_2/toluene, 8/2); **^{1}H NMR** ($CDCl_3$) δ 0.48 (6H, s, $Ge(CH_3)_2$), 1.36 (3H, t, J 7.0, CH_3CH_2O), 1.38 (2H, m, $ArCH_2CH_2Ge$), 2.46 (3H, s, $ArCH_3$), 2.78 (2H, m, $ArCH_2CH_2Ge$), 3.70 (2H, q, J 7.0, CH_3CH_2O), 3.87 (2H, t, J 5.0, OCH_2CH_2OAr), 4.19 (2H, t, J 5.0, OCH_2CH_2OAr), 6.95 (2H, d, J 8.5, $OCCHCHCCH_2$), 7.20 (2H, d, J 8.5, $OCCHCHCCH_2$), 7.30 (2H, d, J 8.0, $GeCCHCHCCH_3$), 7.49 (2H, d, J 8.0, $GeCCHCHCCH_3$); **^{13}C NMR** ($CDCl_3$) δ –3.5 (2q), 15.3 (q), 18.2 (t), 21.5 (q), 30.4 (t), 66.9 (t), 67.6 (t), 69.2 (t), 114.7 (d), 128.8 (d), 129.0 (d), 129.4 (d), 133.4 (d), 137.1 (s), 137.7 (s), 138.1 (s), 157.1 (s); **IR** (neat) 2927, 2869, 1611, 1510, 1246, 1125, 1089, 1067, 795, 593 cm^{-1}; **MS** (EI) *m/z* 388 (7%) (M^{+}), 195 (100%); **HRMS** calc'd for $C_{21}H_{30}O_2{}^{74}Ge$ 388.1458, found 388.1457, error –0.16 ppm; **Elemental analysis** expected for $C_{21}H_{30}O_2Ge$ C 65.17%, H 7.81%, analysis found C 65.14%, H 8.07%.

4-{[2-Dimethyl-(4-methoxyphenyl)germanyl]ethyl}phenyl (2-ethoxyethyl) ether (13)

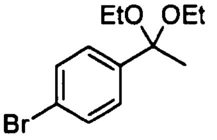


13

Molecular Weight =403.06
Molecular Formula =$C_{21}H_{30}GeO_3$

4-Bromoanisole **12** (0.55mL, 0.823g, 4.4mmol) was dissolved in 10mL anhydrous THF under N_2 and cooled to –78°C. n-BuLi (2.5M in hexanes, 5mmol) was added dropwise and slowly over 10min. The resulting mixture was then stirred for 45 minutes. Chlorodimethylgermane **10** (0.372g, 1.12mmol) was dissolved in 2mL anhydrous THF and then added to the solution of 4-lithioanisole, the CO_2/acetone bath was removed and the solution allowed to warm to rt. Distilled water was added dropwise to destroy any remaining organometallic, and the resulting mixture then extracted between distilled water (10mL) and EtOAc (2 × 10mL). The organic washings were combined, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (16 × 5cm Silica gel, eluted with toluene/ CH_2Cl_2, 8/2) gave anisylgermane **13** as a light brown oil (0.195g, 0.483mmol, 43%). **R*f*** 0.17 (toluene/ CH_2Cl_2, 8/2); **^{1}H NMR** ($CDCl_3$) δ 0.37 (6H, s, $Ge(C\mathit{H}_3)_2$), 1.27 (2H, m, *J* 9.0, $ArCH_2C\mathit{H}_2Ge$), 1.27 (3H, t, *J* 7.0, $C\mathit{H}_3CH_2O$), 2.67 (2H, m, *J* 9.0, $ArC\mathit{H}_2CH_2Ge$), 3.66 (2H, q, *J* 7.0, $CH_3C\mathit{H}_2O$), 3.8 (2H, t, *J* 5.0, $OC\mathit{H}_2CH_2OAr$), 4.12 (2H, t, *J* 5.0, $OCH_2C\mathit{H}_2OAr$), 6.86 (2H, d, *J* 8.5, $OCC\mathit{H}CHCCH_2$), 6.94 (2H, d, *J* 8.5, $GeCCHC\mathit{H}COCH_3$), 7.11 (2H, d, *J* 8.5, $OCCHC\mathit{H}CCH_2$), 7.41 (2H, d, *J* 8.5, $GeCC\mathit{H}CHCOCH_3$); **^{13}C NMR** ($CDCl_3$) δ -3.6 (q), 15.2 (q), 18.2 (t), 30.2, 55.1 (q), 66.8 (t), 67.7 (t), 69.1 (t), 113.8 (d), 114.6 (d), 128.7 (d), 132.0 (s), 134.4 (d), 137.1 (s), 156.9 (s), 159.9 (s); **IR** (neat) 2930, 1592, 1510, 1279, 1247, 1180, 1125, 1093, 1032, 922, 821, 600 cm^{-1}; **MS** (EI) *m/z* 404 (6%, M^{+}), 389 (10%), 296 (25%), 281 (15%), 211 (100%), 121 (58%), 107 (78%); **HRMS** calc'd for $C_{21}H_{30}{}^{74}GeO_3$ 404.1407, found 404.1410, error −1.0ppm; **Elemental analysis** expected for $C_{21}H_{30}GeO_2$ C 62.58%, H 7.50%, analysis found C 62.59%, H 7.75%.

1-Bromo-4-(1,1-diethoxyethyl)benzene (15)[182]



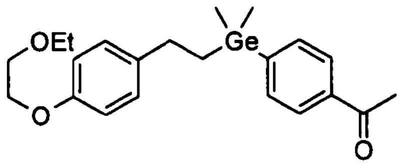
15

Molecular Weight =273.17
Molecular Formula =$C_{12}H_{17}BrO_2$

4-Bromoacetophenone **14** (1.289g, 6.47mmol) was added to a flame-dried round bottom flask, placed under N_2, and dissolved in anhydrous EtOH (20mL). Triethyl orthoformate (2.2mL, 1.96g, 13.2mmol) was added *via* syringe, then NBS (0.0283g, 0.0159mmol) was added. The mixture was stirred at rt for 17 hours, before adding aqueous NaOH (2M, 30mL), followed by Et_2O (70mL). The phases were separated and the aqueous layer extracted with Et_2O (2 × 50mL). The organic washings were combined, dried with $MgSO_4$ and concentrated *in vacuo* to give diethyl acetal **15** as a colourless oil (1.64g, 6.01mmol, 93%). **R*f*** 0.91 (Petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 1.21 (6H, t, *J* 7.0, $OCH_2C\mathit{H}_3$), 1.53 (3H, s, $ArC(OEt)_2C\mathit{H}_3$), 3.41 (4H, m, $OC\mathit{H}_2CH_3$), 7.40 (2H, d, *J* 9.0, Ar CH's), 7.47 (2H, d, *J* 9.0, Ar CH's); **MS** (EI) *m/z*

274 ($M^{\cdot+}$ 1%), 259 (2%), 227 (39%), 200 (27%), 183 (100%), 157 (23%), 147 (24%), 103 (43%), 75 (48%).

4-{[2-Dimethyl-(4-acetophenyl)germanyl]ethyl}phenyl (2-ethoxy-ethyl) ether (16)



16

Molecular Weight =415.07
Molecular Formula =$C_{22}H_{30}GeO_3$

Diethyl acetal **15** (4.84g, 17.9mmol) was dissolved in anhydrous THF (50mL) under a nitrogen atmosphere and cooled to –78°C. n-BuLi (7mL, 2.5M in hexanes, 17.5mmol) was added slowly and dropwise in 1mL portions to the cooled solution with stirring. The resulting mixture was stirred at –78°C for 1 hour.

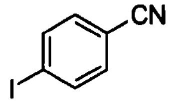
Chlorodimethylgermane **11** (2.24g, 6.76mmol) was dissolved in anhydrous THF (4mL) and added dropwise to the solution of the aryl lithium. The resulting mixture was stirred at -78°C for 30 minutes, before the CO_2/acetone bath was removed and the solution allowed to warm to rt over 17 hours.

Aqueous HCl (1M, 20mL) was added, and the mixture was then partitioned between distilled water (100mL) and Et_2O (100mL). The aqueous layer was further extracted with Et_2O (2 × 50mL). The organic washings were combined and dried with $MgSO_4$, before being filtered and concentrated *in vacuo*.

The crude mixture was then dissolved in distilled acetone (95mL). Distilled water (10mL) and PPTS (0.215g, 0.854mmol) were added to the solution, which was then refluxed for 17 hours. Solvent was removed *in vacuo*, and the resulting crude mixture partitioned between EtOAc (100mL) and distilled water (100mL). The aqueous layer was further extracted with EtOAc (2 × 50mL), and organic layers were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20 × 5cm Silica gel, eluted with petrol/EtOAc, 9/1) gave acetophenylgermane **16** as a light brown oil (2.41g, 5.81mmol, 86%). $\mathbf{R}_f$ 0.25

(petrol/EtOAc, 9/1); ^{1}**H NMR** ($CDCl_3$) δ 0.39 (6H, s, $Ge(CH_3)_2$), 1.25 (3H, t, *J* 7.0, $C\mathit{H}_3CH_2O$), 1.30 (2H, m, *J* 8.5, $CH_2C\mathit{H}_2Ge$), 2.62 (3H, s, $COC\mathit{H}_3$), 2.65 (2H, m, *J* 8.5, $C\mathit{H}_2CH_2Ge$), 3.61 (2H, q, *J* 7.0, $CH_3C\mathit{H}_2O$), 3.78 (2H, t, *J* 5.0, $OC\mathit{H}_2CH_2OAr$), 4.10 (2H, t, *J* 5.0, $OCH_2C\mathit{H}_2OAr$), 6.83 (2H, d, *J* 9.0, $OCC\mathit{H}CHCCH_2$), 7.06 (2H, d, *J* 9.0, $OCCHC\mathit{H}CCH_2$), 7.56 (2H, d, *J* 8.0, $GeCC\mathit{H}CHCCOCH_3$), 7.92 (2H, d, *J* 8.0, $GeCCHC\mathit{H}CCOCH_3$); ^{13}**C NMR** ($CDCl_3$) δ -3.8 (q), 15.2 (q), 17.9 (t), 26.6(q), 30.1 (t), 66.8 (t), 67.5 (t), 69.0 (t), 114.6 (d), 127.4 (d), 128.7 (d), 133.4 (d), 136.5 (s), 136.9 (s), 148.7 (s), 157.0 (s), 198.4 (s); **IR** (neat) 2930, 1683, 1511, 1389, 1246, 1124, 1065, 955, 819, 604 cm^{-1}; **MS** (EI) *m/z* 416 (M^+ 13%), 401 (12%), 296 (19%), 277 (27%), 254 (47%), 223 (55%), 211 (100%), 193 (39%); **HRMS** calc'd for $C_{22}H_{30}{}^{74}GeO_3$ 416.1407, found 416.1415, error −1.9 ppm; **Elemental analysis** expected for $C_{22}H_{30}GeO_3$ C 63.66%, H 7.29%, analysis found C 63.44%, H 7.52%.

4-Iodobenzonitrile (18)[183]



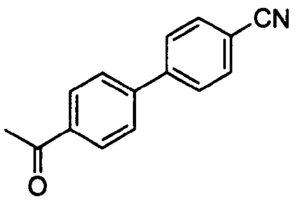
18

Molecular Weight =229.02
Molecular Formula =C_7H_4IN

4-Aminobenzonitrile (0.0997g, 0.843mmol) was dissolved in aqueous sulfuric acid (2.5M, 1.4mL) and cooled in an ice/salt bath. $NaNO_2$ (0.0675g, 0.978mmol) was dissolved in distilled water (0.5mL) and added to the acidic solution, which was then stirred at −5°C for 30 minutes. Sodium iodide (0.316g, 2.11mmol) was added to the diazonium compound and the mixture warmed to rt. The resulting foam and solution were diluted with distilled water (20mL) and extracted with EtOAc (2 × 10mL). The organic layer was then washed with saturated aqueous $Na_2S_2O_3$ (15mL), and saturated aqueous $NaHCO_3$ (15mL), before being dried with $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5 × 10cm Silica gel, eluted with petrol/EtOAc, 9/1) gave 4-iodobenzonitrile **18** as white crystals (0.124g, 0.540mmol, 64%). **R*f*** 0.58 (petrol/EtOAc, 9/1); ^{1}**H NMR** ($CDCl_3$) δ 7.37 (2H, d, *J* 8.5, $ICCHC\mathit{H}CCN$), 7.84 (2H, d, *J* 8.5, $ICC\mathit{H}CHCCN$); **MS** (EI) *m/z* 229 (40%, M^+), 102 (100%); **Melting point** 128.3-129.9°C (*cf.* 124-125.5°C[212]).

General method for the synthesis of biaryls by Suzuki coupling:

4-Acetyl-4'cyano-biphenyl (29)[213]

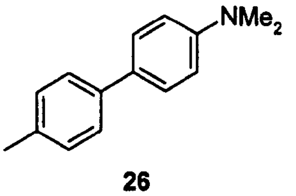


29

Molecular Weight =221.26
Molecular Formula =$C_{15}H_{11}NO$

4-Bromobenzonitrile (0.366g, 2mmol), and $Pd(PPh_3)_4$ (0.118g, 0.1mmol) were added to a carousel reaction tube, placed under an N_2 atmosphere, and dissolved in anhydrous toluene (4mL). Aqueous NaOH (2M, 2mL), and 4-acetophenyl boronic acid (0.366g, 2.2mmol) in anhydrous EtOH (1mL) were then added to the reaction tube, which was heated at 90°C for 17 hours. The reaction mixture was partitioned between Et_2O (2 × 10mL) and distilled water (10mL), the organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5 × 15 cm Silica gel, eluted with petrol/EtOAc, 19/1) gave 4-acetyl-4'-cyano-biphenyl **29** as an off-white powder (0.285g, 1.29mmol, 64%). **R_f** 0.16 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 2.65 (3H, s, COC*H*$_3$), 7.69 (2H, d, *J* 9.0, CNCC*H*CHC), 7.72 (2H, d, *J* 9.0, CC*H*CHCCOCH$_3$), 7.77 (2H, d, *J* 9.0, CNCCHC*H*C), 8.07 (2H, d, *J* 9.0, CCHC*H*CCOCH$_3$); **MS** *m/z* (EI) 221 (M^+ 32%), 206 (100%), 178 (24%), 151 (34%), 75 (9%); **GC/MS R_t** 8.53min; **Melting point** 107.5-109.8°C (*cf.* 117-120°C[214]).

4-N,N-Dimethylamino-4'-methyl-biphenyl (26)[215]

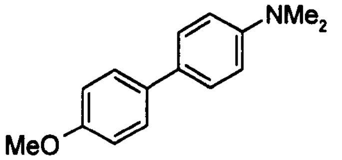


26

Molecular Weight =211.31
Molecular Formula =$C_{15}H_{17}N$

The above general method, using 4-bromo-*N*,*N*-dimethylaniline (0.402g, 2.01mmol), $Pd(PPh_3)_4$ (0.119g, 0.102mmol), and 4-methylphenyl boronic acid (0.301g, 2.21mmol) was employed. Purification by column chromatography (5 × 15cm silica gel, eluted with petrol/EtOAc, 9/1) gave 4-*N*,*N*-dimethylamino-4'methylbiphenyl **26** as white needles (0.0936g, 0.443mmol, 22%). **R*f*** 0.76 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 2.37 (3H, s, $ArCH_3$), 2.98 (6H, s, $N(CH_3)_2$), 6.80 (2H, d, *J* 9.0, CCHC*H*CN(CH_3)$_2$), 7.20 (2H, d, *J* 8.0, CH_3CC*H*CHC), 7.45 (2H, d, *J* 8.0, CH_3CCHC*H*C), 7.48 (2H, d, *J* 9.0, CC*H*CHCN(CH_3)$_2$); **MS** (EI) m/z 211(M^{+} 100%), 195 (13%), 165 (14%), 152 (16%), 106 (12%); **GC/MS R*t*** 6.87min; **Melting point** 130.6-135.3°C (*cf.* 120-122°C[216]).

4-N,N-Dimethylamino-4'-methoxy-biphenyl (27)[217]

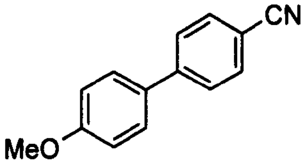


27

Molecular Weight =227.31
Molecular Formula =$C_{15}H_{17}NO$

The above general method, using 4-bromo-*N*,*N*-dimethylaniline (0.401g, 2.00mmol), $Pd(PPh_3)_4$ (0.121g, 0.104mmol), and 4-methoxyphenyl boronic acid (0.338g, 2.22mmol) was employed. Purification by column chromatography, (toluene/ CH_2Cl_2, 8/2) gave 4-*N*,*N*-dimethylamino-4'-methoxy-biphenyl **27** as a brown powder (0.0731g, 0.322mmol, 16%). **R*f*** 0.35 (toluene/ CH_2Cl_2, 8/2); **^{1}H NMR** ($CDCl_3$) δ 2.99 (6H, s, N(C*H*$_3$)$_2$), 3.85 (3H, s, OC*H*$_3$), 6.82 (2H, d, *J* 9.0, CCHC*H*CN(CH_3)$_2$), 6.96 (2H, d, *J* 9.0, CH_3OCC*H*CHC), 7.47 (2H, d, *J* 9.0, Ar CH's), 7.49 (2H, d, *J* 9.0, Ar CH's); **MS** (EI) *m/z* 227(M^{+} 100%), 212 (99%), 184 (19%), 168 (10%), 113 (14%); **GC/MS R*t*** 8.39min; **Melting point** 153.7-154.7°C (*cf.* 157°C[218]).

4-Cyano-4'-methoxy-biphenyl (28)[219]

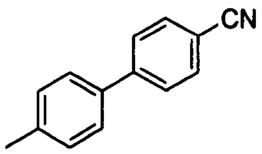


28

Molecular Weight =209.25
Molecular Formula =$C_{14}H_{11}NO$

The above general method, using 4-bromobenzonitrile (0.370g, 2.03mmol), $Pd(PPh_3)_4$ (0.120g, 0.104mmol), and 4-methoxyphenyl boronic acid (0.339g, 2.23mmol) was employed. Purification by column chromatography, (Petrol/EtOAc, 9/1) gave 4-cyano-4'-methoxy-biphenyl **28** as white needles (0.162g, 0.775mmol, 38%). **R*f*** 0.29 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 3.88 (3H, s, OC*H*$_3$), 7.02 (2H, d, *J* 9.0, Ar CH's), 7.55 (2H, d, *J* 9.0, Ar CH's), 7.65 (2H, d, *J* 9.0, Ar CH's), 7.71 (2H, d, *J* 9.0, Ar CH's); **MS** (EI) *m/z* 209($M^{\cdot+}$ 100%), 194 (34%), 166 (57%), 140 (37%); **GC/MS R*t*** 7.12min; **Melting point** 105.4-107.8°C (*cf.* 103-104°C[98]).

4-Cyano-4'-methyl-biphenyl (3)[184]



3

Molecular Weight =193.25
Molecular Formula =$C_{14}H_{11}N$

To a three necked round bottom flask fitted with a condenser, a septum, a solids addition tube charged with 4-bromobenzonitrile (0.426g, 2.34mmol) and $Pd(PPh_3)_4$ (0.118g, 0.102mmol, 4.3mol%), was added 4-bromotoluene (1.01g, 5.89mmol) in THF (8mL) under an argon atmosphere. The solution of 4-bromotoluene was cooled to –78°C, t-BuLi (7.8mL, 11.7mmol, 1.5M in pentane) added dropwise and then the mixture was stirred for 30min at –78°C. A solution of $ZnCl_2$ (0.829g, 6.08mmol) in THF (15mL) was then added *via* syringe. The CO_2/acetone bath was removed and the resulting mixture warmed to rt with stirring over 1h. The solids addition tube was inverted to add the aryl bromide and catalyst, and the mixture heated at 70°C for 2.5h. The reaction mixture was then quenched with H_2O (50mL) and partitioned between 1M HCl (200mL) and EtOAc (200mL). The aqueous layer was further extracted with EtOAc (3 × 100mL). The organic washings were combined, dried with $MgSO_4$, and evaporated. The resulting brown crystals were recrystallised (isopropanol) to give a 1:1 mixture of desired product **3** and 4,4'-dimethyl-biphenyl by ^{1}H NMR. Purification by flash chromatography (5 × 15 cm silica gel, eluted with petrol/EtOAc, 19/1) gave 4-cyano-4'-methyl-biphenyl **3** as white needles (0.158g, 0.819mmol, 35%). **R*f*** 0.32 (petrol/EtOAc, 19/1); **^{1}H NMR** ($CDCl_3$) δ 2.41 (3H, s, ArCH$_3$), 7.28 (2H, d, *J* 8.0, CH$_3$CC*H*CHC), 7.49 (2H, d, *J* 8.0, CH$_3$CCHC*H*C), 7.67 (2H, d, *J* 8.5, CCHC*H*CCN), 7.70 (2H, d, *J* 8.5, CC*H*CHCCN); **MS** (EI) *m/z* 193 ($M^{\cdot+}$ 100%), 190

(14%), 178 (8%), 165 (19%); **GC/MS R_t**.7.68min; **Melting point** 105-106°C (*cf.* 104-107°C[184]).

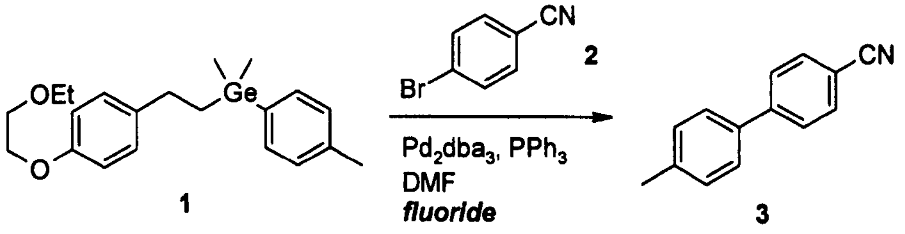
Authentic product response factor calculations

The authentic product and naphthalene standard were weighed out into a 10mL volumetric flask and dissolved in DMF. The resulting solution was analysed by GC/MS three consecutive times, and the average ratio of standard area/product area from the integrated TIC was used to calculate the response factor.

Product		Standard	Product	Molar ratio standard/ product	Area ratio standard/ product	Response factor
4-Me, 4'-CN	**3**	0.0103g, 0.0804mmol	0.0102g, 0.0528mmol	1.522	0.4787	0.314 (± 0.003)
4-Me	**19**	0.0120g, 0.0936mmol	0.0126g, 0.0749mmol	1.250	1.141	0.913 (± 0.007)
4-OMe	**20**	0.0137g, 0.107mmol	0.0136g, 0.0738mmol	1.448	1.206	0.833 (± 0.006)
4-Ac	**21**	0.0117g, 0.0913mmol	0.0131g, 0.0668mmol	1.367	0.6942	0.508 (± 0.004)
4-Me, 4'-NMe_2	**26**	0.0114g, 0.0889mmol	0.0110g, 0.0521mmol	1.708	0.8758	0.513 (± 0.004)
4-OMe, 4'-NMe_2	**27**	0.0113g, 0.0882mmol	0.0112g, 0.0493mmol	1.789	1.410	0.788 (± 0.006)
4-OMe, 4'-CN	**28**	0.0116g, 0.0905mmol	0.0103g, 0.0492mmol	1.839	1.256	0.683 (± 0.006)
4-Ac, 4'-CN	**29**	0.0144g, 0.112mmol	0.0127g, 0.0574mmol	1.957	1.091	0.557 (± 0.004)

6.2.1.2 Cross-coupling: Scanning experiment

Initial fluoride experiments (Figure 4.10 and Table 4.2)



General method

A 3mL reaction vial was charged with tolylgermane **1**, 4-bromobenzonitrile, $Pd_2(dba)_3$, PPh_3, and fluoride. The reagents were dissolved in DMF (1mL), sealed and heated at 130°C for 48 hours. The reaction mixture was sampled and analysed by quantitative GC/MS with naphthalene internal standard to give the following results.

Coupling with KF + 18-crown-6 activator

Tolylgermane **1** (0.0993g, 0.257mmol), 4-bromobenzonitrile (0.0555g, 0.305mmol), $Pd_2(dba)_3$ (0.0054g, 0.00590mmol), PPh_3 (0.0060g, 0.0230mmol), KF (0.0313g, 0.538mmol), 18-crown-6 (0.145g, 0.550mmol). Naphthalene (0.0087g, 0.0680mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R$_t$** 7.58min; **yield** 8%.

Coupling with KF activator

Tolylgermane **1** (0.0919g, 0.237mmol), 4-bromobenzonitrile (0.0517g, 0.284mmol), $Pd_2(dba)_3$ (0.0057g, 0.0062mmol), PPh_3 (0.0060g, 0.023mmol), KF (0.0352g, 0.605mmol). Naphthalene (0.0107g, 0.0836mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R$_t$** 7.58min; **yield** 13%.

Coupling with TBAF.3H$_2$O activator

Tolylgermane **1** (0.0925g, 0.239mmol), 4-bromobenzonitrile (0.0524g, 0.289mmol), $Pd_2(dba)_3$ (0.0053g, 0.0059mmol), PPh_3 (0.0059g, 0.023mmol), TBAF.3H_2O (0.178g, 0.564mmol. Naphthalene (0.0119g, 0.0930mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R$_t$** 7.58min; **yield** 0.1%.

Coupling with BnTMAF activator

Tolylgermane **1** (0.0989g, 0.256mmol), 4-bromobenzonitrile (0.0539g, 0.296mmol), $Pd_2(dba)_3$ (0.0060g, 0.0066mmol), PPh_3 (0.0064g, 0.024μmol), BnTMAF (0.0881g, 0.521mmol). Naphthalene (0.0119g, 0.0930mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R$_t$** 7.58min; **yield** 32%. Purification by column chromatography (8 × 3cm Silica gel, CH_2Cl_2/petrol, 8/2) gave 4-cyano-4'-methyl-biphenyl as off white needles (0.0109g, 0.0563mmol, 22%). Analytical data as above.

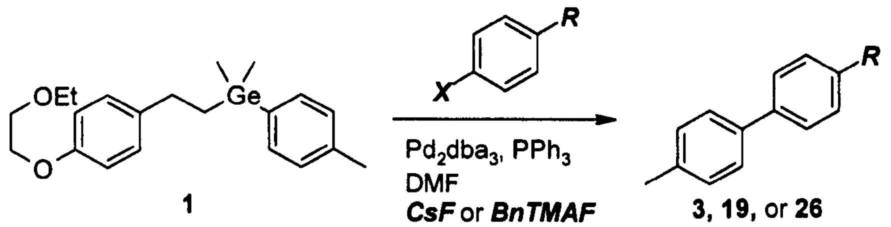
Coupling with CsF activator

Tolylgermane **1** (0.0999g, 0.258mmol), 4-bromobenzonitrile (0.0565g, 0.310mmol), $Pd_2(dba)_3$ (0.0114g, 0.0124mmol), PPh_3 (0.0136g, 0.0519mmol), and CsF (0.175g, 1.15mmol). Naphthalene (0.0109g, 0.0852mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R$_t$** 7.58min; **yield** 7%.

Coupling with KF + 18-crown-6 activator at 150 °C

Tolylgermane **1** (0.0948g, 0.245mmol), 4-bromobenzonitrile (0.0552g, 0.303mmol), $Pd_2(dba)_3$ (0.0055g, 0.00601mmol), PPh_3 (0.0063g, 0.0240mmol), KF (0.0330g, 0.568mmol) and 18-crown-6 (0.146g, 0.554mmol). Naphthalene (0.0164g, 0.128mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R$_t$** 7.58min; **yield** 15%.

Scanning experiment: Tolylgermane cross-couplings (Figure 4.11)



General method

A 3mL reaction vial was charged with tolylgermane **1**, aryl halide, $Pd_2(dba)_3$, PPh_3, and fluoride. The reagents were dissolved in DMF (1mL), sealed and heated at 150°C for 48 hours. Naphthalene solution (0.01mL, 0.25M) was added to a 25μL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS gave the following results.

Scanning experiment general method: Coupling with 4-bromobenzonitrile and BnTMAF

Tolylgermane **1** (0.107g, 0.276mmol), 4-bromobenzonitrile (0.0597g, 0.328mmol), $Pd_2(dba)_3$ (0.0062g, 0.00677mmol), PPh_3 (0.0072g, 0.0275mmol), BnTMAF (0.0872g, 0.515mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R_t** 7.58min; **yield** 1%.

Coupling with 4-bromobenzonitrile and CsF

Tolylgermane **1** (0.104g, 0.269mmol), 4-bromobenzonitrile (0.0590g, 0.324mmol), $Pd_2(dba)_3$ (0.0062g, 0.00677mmol), PPh_3 (0.0072g, 0.0275mmol) and CsF (0.110g, 0.724mmol. 4-Cyano-4'-methyl-biphenyl: **GC/MS R_t** 7.57min; **yield** 33%.

Coupling with 4-iodobenzonitrile and BnTMAF

Tolylgermane **1** (0.104g, 0.269mmol), 4-iodobenzonitrile (0.0816g, 0.356mmol), $Pd_2(dba)_3$ (0.0063g, 0.00688mmol), PPh_3 (0.0070g, 0.0267mmol) and BnTMAF (0.102g, 0.603mmol): 4-Cyano-4'-methyl-biphenyl not observed.

Coupling with 4-iodobenzonitrile and CsF

Tolylgermane **1** (0.100g, 0.258mmol), 4-iodobenzonitrile (0.0832g, 0.363mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), PPh_3 (0.0067g, 0.0255mmol) and CsF (0.0840g, 0.553mmol): 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.57min; **yield** 4%.

Coupling with bromobenzene and BnTMAF

Tolylgermane **1** (0.101g, 0.261mmol), bromobenzene (33μL, 0.0494g, 0.315mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), PPh_3 (0.0069g, 0.0263mmol) and BnTMAF (0.106g, 0.626mmol). 4-Methyl-biphenyl: **GC/MS R_t** 3.54min; **yield** 31%.

Coupling with iodobenzene and BnTMAF

Tolylgermane **1** (0.101g, 0.261mmol), iodobenzene (35μL, 0.0639g, 0.313mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), PPh_3 (0.0068g, 0.0259mmol) and BnTMAF (0.136g, 0.804mmol). 4-Methyl-biphenyl was not observed.

Coupling with iodobenzene and CsF

Tolylgermane **1** (0.0607g, 0.157mmol), iodobenzene (35μL, 0.0639g, 0.313mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), PPh_3 (0.0068g, 0.0259mmol) and CsF (0.136g, 0.895mmol). 4-Methyl-biphenyl: **GC/MS R_t** 3.55min; **yield** 8%.

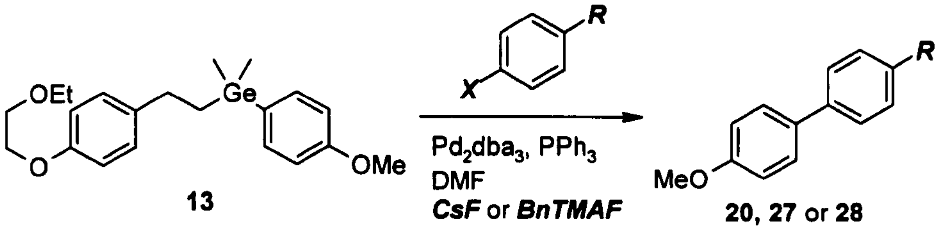
Coupling with 4-bromo-N,N-dimethylaniline and BnTMAF

Tolylgermane **1** (0.0998g, 0.258mmol), 4-bromo-*N,N*-dimethylaniline (0.0628g, 0.314mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), PPh_3 (0.0068g, 0.0259mmol) and BnTMAF (0.102g, 0.603mmol). 4-*N,N*-Dimethylamino-4'-methyl-biphenyl: **GC/MS R_t** 9.75min; **yield** 8%.

Coupling with 4-bromo-N,N-dimethylaniline and CsF

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromo-*N,N*-dimethylaniline (0.0638g, 0.319mmol), $Pd_2(dba)_3$ (0.0063g, 0.00688mmol), PPh_3 (0.0069g, 0.0263mmol) and CsF (0.0949g, 0.625mmol). 4-*N,N*-Dimethylamino-4'-methyl-biphenyl was not observed.

Scanning experiment: Anisylgermane cross-coupling general method (Figure 4.12)



General method

A 3mL reaction vial was charged with anisylgermane **13**, aryl halide, $Pd_2(dba)_3$, PPh_3, and fluoride. The reagents were dissolved in DMF (1.5mL), sealed and heated at 150°C for 48 hours. Naphthalene solution (0.01mL, 0.25M) was added to a 25μL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS gave the following results.

Coupling with 4-bromobenzonitrile and BnTMAF

Anisylgermane **13** (0.104g, 0.257mmol), 4-bromobenzonitrile (0.0588g, 0.323mmol), $Pd_2(dba)_3$ (0.0058g, 0.00633mmol), PPh_3 (0.0064g, 0.0244mmol) and BnTMAF (0.101g, 0.597mmol). 4-Cyano-4'-methoxy-biphenyl: **GC/MS R_f** 10.19min; **yield** 0.7%.

Coupling with 4-bromobenzonitrile and CsF

Anisylgermane **13** (0.104g, 0.258mmol), 4-bromobenzonitrile (0.0579g, 0.318mmol), $Pd_2(dba)_3$ (0.0059, 0.00644mmol), PPh_3 (0.0065g, 0.0248mmol) and CsF (0.0789g, 0.519mmol). 4-Cyano-4'-methoxy-biphenyl: **GC/MS R_f** 10.23min; **yield** 28%.

Coupling with 4-iodobenzonitrile and BnTMAF

Anisylgermane **13** (0.104g, 0.258mmol), 4-iodobenzonitrile (0.0745g, 0.325mmol), $Pd_2(dba)_3$ (0.0061g, 0.00666mmol), PPh_3 (0.0063g, 0.0240mmol) and BnTMAF (0.0956g, 0.565mmol) dissolved in. 4-Cyano-4'-methoxy-biphenyl was not observed.

Coupling with 4-iodobenzonitrile and CsF

Anisylgermane **13** (0.104g, 0.257mmol), 4-iodobenzonitrile (0.0713g, 0.311mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), PPh_3 (0.0066g, 0.0252mmol) and CsF (0.0848g, 0.558mmol). 4-Cyano-4'-methoxy-biphenyl: **GC/MS R$_t$** 10.18min; **yield** 2.5%.

Coupling with bromobenzene and BnTMAF

Anisylgermane **13** (0.103g, 0.255mmol), bromobenzene (33µL, 0.0494g, 0.315mmol), $Pd_2(dba)_3$ (0.0058g, 0.00633mmol), PPh_3 (0.0065g, 0.0248mmol) and BnTMAF (0.0938g, 0.554mmol). 4-Methoxy-biphenyl: **GC/MS R$_t$** 5.11min; **yield** 19%.

Coupling with bromobenzene and CsF

Anisylgermane **13** (0.104g, 0.259mmol), bromobenzene (33µL, 0.0494g, 0.315mmol), $Pd_2(dba)_3$ (0.0058g, 0.00633mmol), PPh_3 (0.0065g, 0.0248mmol) and CsF (0.0820g, 0.540mmol). 4-Methoxy-biphenyl: **GC/MS R$_t$** 5.10min; **yield** 1.3%.

Coupling with iodobenzene and BnTMAF

Anisylgermane **13** (0.105g, 0.259mmol), iodobenzene (35µL, 0.0639g, 0.313mmol), $Pd_2(dba)_3$ (0.0058g, 0.00633mmol), PPh_3 (0.0063g, 0.0240mmol) and BnTMAF (0.0872g, 0.515mmol). 4-Methoxy-biphenyl: **GC/MS R$_t$** 5.11min; **yield** 1.3%.

Coupling with iodobenzene and CsF

Anisylgermane **13** (0.104g, 0.258mmol), iodobenzene (35µL, 0.0639g, 0.313mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), PPh_3 (0.0066g, 0.0252mmol) and CsF (0.0869g, 0.572mmol). 4-Methoxy-biphenyl: **GC/MS R$_t$** 5.11min; **yield** 4%.

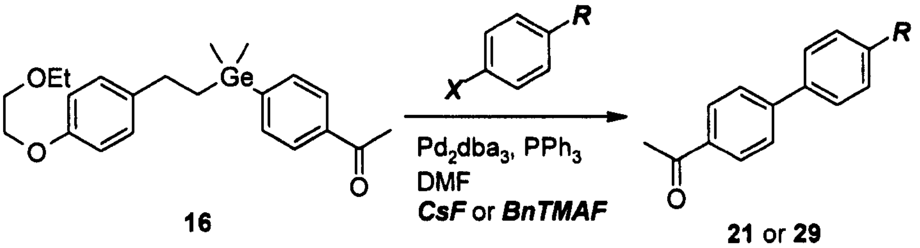
Coupling with 4-bromo-N,N-dimethylaniline and BnTMAF

Anisylgermane **13** (0.105g, 0.259mmol), 4-bromo-*N*,*N*-dimethylaniline (0.645g, 0.322mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), PPh_3 (0.0065g, 0.0248mmol) and BnTMAF (0.105g, 0.620mmol). 4-*N*,*N*-Dimethylamino-4'-methoxy-biphenyl: **GC/MS R$_t$** 12.35min; **yield** 16%.

Coupling with 4-bromo-N,N-dimethylaniline and CsF

Anisylgermane **13** (0.105g, 0.260mmol), 4-bromo-*N*,*N*-dimethylaniline (0.0642g, 0.321mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), PPh_3 (0.0066g, 0.0252mmol) and CsF (0.0935g, 0.616mmol). 4-*N*,*N*-Dimethylamino-4'-methoxy-biphenyl was not observed.

Scanning experiment: Acetophenylgermane cross-couplings (Figure 4.13)



General method

A 3mL reaction vial was charged with acetophenylgermane **16**, aryl halide, $Pd_2(dba)_3$, PPh_3, and fluoride. The reagents were dissolved in DMF (1.5mL), sealed and heated at 150°C for 48 hours. Naphthalene solution (0.01mL, 0.25M) was added to a 25μL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS gave the following results.

Coupling with 4-bromobenzonitrile and BnTMAF

Acetophenylgermane **16** (0.109g, 0.263mmol), 4-bromobenzonitrile (0.0588g, 0.323mmol), $Pd_2(dba)_3$ (0.0061g, 0.00666mmol), PPh_3 (0.0070g, 0.0267mmol) and BnTMAF (0.0880g, 0.520mmol). 4-Acetyl-4'cyano-biphenyl: **GC/MS R*f*** 12.93min; **yield** 3%.

Coupling with 4-bromobenzonitrile and CsF

Acetophenylgermane **16** (0.108g, 0.259mmol), 4-bromobenzonitrile (0.0567g, 0.311mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), PPh_3 (0.0069g, 0.0263mmol) and CsF (0.149g, 0.981mmol). 4-Acetyl-4'cyano-biphenyl: **GC/MS R*f*** 12.90min; **yield** 15%.

Coupling with 4-iodobenzonitrile and BnTMAF

Acetophenylgermane **16** (0.107g, 0.257mmol), 4-iodobenzonitrile (0.0779g, 0.340mmol), $Pd_2(dba)_3$ (0.0058g, 0.00633mmol), PPh_3 (0.0068g, 0.0259mmol) and BnTMAF (0.0973g, 0.574mmol). 4-Acetyl-4'cyano-biphenyl was not observed.

Coupling with 4-iodobenzonitrile and CsF

Acetophenylgermane **16** (0.107g, 0.259mmol), 4-iodobenzonitrile (0.0825g, 0.360mmol), $Pd_2(dba)_3$ (0.0064g, 0.00699mmol), PPh_3 (0.0072g, 0.0275mmol) and CsF (0.0825g, 0.543mmol). 4-Acetyl-4'cyano-biphenyl: **GC/MS R$_t$** 12.90min; **yield** 13%.

Coupling with bromobenzene and BnTMAF

Acetophenylgermane **16** (0.108g, 0.260mmol), bromobenzene (33μL, 0.0494g, 0.315mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), PPh_3 (0.0068g, 0.0259mmol) and BnTMAF (0.102g, 0.605mmol). 4-Acetyl-biphenyl: **GC/MS R$_t$** 7.30min; **yield** 7%.

Coupling with bromobenzene and CsF

Acetophenylgermane **16** (0.108g, 0.260mmol), bromobenzene (33μL, 0.0494g, 0.315mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), PPh_3 (0.0070g, 0.0267mmol) and CsF (0.100g, 0.660mmol). 4-Acetyl-biphenyl: **GC/MS R$_t$** 7.30min; **yield** 1.0%.

Coupling with iodobenzene and BnTMAF

Acetophenylgermane **16** (0.108g, 0.260mmol), iodobenzene (35μL, 0.0639g, 0.313mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), PPh_3 (0.0066g, 0.0229mmol) and BnTMAF (0.103g, 0.610mmol). 4-Acetyl-biphenyl: **GC/MS R$_t$** 7.29min; **yield** 2.5%.

Coupling with iodobenzene and CsF

Acetophenylgermane **16** (0.108g, 0.260mmol), iodobenzene (35μL, 0.0639g, 0.313mmol), $Pd_2(dba)_3$ (0.0057g, 0.00622mmol), PPh_3 (0.0065g, 0.0248mmol) and CsF (0.0983g, 0.647mmol). 4-Acetyl-biphenyl: **GC/MS R$_t$** 7.32min; **yield** 11%.

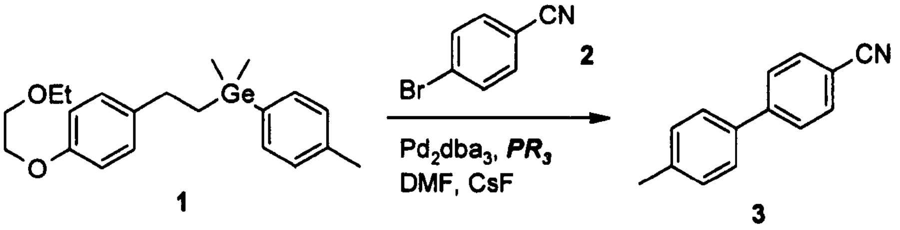
Coupling with 4-bromo-N,N-dimethylaniline and BnTMAF

Acetophenylgermane **16** (0.108g, 0.260mmol), 4-bromo-*N*,*N*-dimethylaniline (0.0620g, 0.310mmol), $Pd_2(dba)_3$ (0.0061g, 0.00666mmol), PPh_3 (0.0069g, 0.0263mmol) and BnTMAF (0.0995g, 0.588mmol). 4-Acetyl-4'-*N*,*N*-dimethylamino-biphenyl was not observed.

Coupling with 4-bromo-N,N-dimethylaniline and CsF

Acetophenylgermane **16** (0.108g, 0.260mmol), 4-bromo-*N*,*N*-dimethylaniline (0.0637g, 0.318mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), PPh_3 (0.0068g, 0.0259mmol) and CsF (0.0926g, 0.610mmol). 4-Acetyl-4'-*N*,*N*-dimethylamino-biphenyl was not observed.

6.2.1.3 Cross-coupling: Phosphine screen (Figure 4.15)



General method

A 3mL reaction vial was charged with tolylgermane **16**, 4-bromobenzonitrile, $Pd_2(dba)_3$, phosphine, and CsF. The reagents were dissolved in DMF (1.5mL), sealed and heated at 150°C for 48 hours. Naphthalene solution (0.01mL, 0.25M) was added to a 25μL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS gave the following results.

Coupling with triphenylphosphine co-catalyst

Tolylgermane **1** (0.0995g, 0.257mmol), 4-bromobenzonitrile (0.0569g, 0.313mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), PPh_3 (0.0066g, 0.0252mmol) and CsF (0.0859g, 0.566mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R_t** 7.49min; **yield** 0.7%.

Coupling with tri(o-tolyl)phosphine co-catalyst

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0569g, 0.313mmol), $Pd_2(dba)_3$ (0.0062g, 0.00677mmol), P(*o*-Tol)$_3$ (0.0080g, 0.0263mmol) and CsF (0.0875g, 0.576mmol). 4-Cyano-4'-methyl-biphenyl was not observed.

Coupling with tri-2-furylphosphine co-catalyst

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0563g, 0.309mmol), $Pd_2(dba)_3$ (0.0061g, 0.00666mmol), $P(2\text{-furyl})_3$ (0.0061g, 0.0263mmol) and CsF (0.804g, 0.529mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R_t** 7.46min; **yield** 0.1%.

Coupling with tri-(4-fluorophenyl)phosphine co-catalyst

Tolylgermane **1** (0.0995g, 0.257mmol), 4-bromobenzonitrile (0.0571g, 0.314mmol), $Pd_2(dba)_3$ (0.0058g, 0.00633mmol), $P(p\text{-}C_6H_4F)_3$ (0.0078g, 0.0247mmol) and CsF (0.116g, 0.764mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R_t** 7.48min; **yield** 0.4%.

Coupling with tri-(4-trifluoromethyl)phenylphosphine co-catalyst

Tolylgermane **1** (0.0996g, 0.257mmol), 4-bromobenzonitrile (0.0556g, 0.305mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), $P(p\text{-}C_6H_4CF_3)_3$ (0.0120g, 0.0257mmol) and CsF (0.0932g, 0.614mmol). 4-Cyano-4'-methyl-biphenyl: **GC/MS R_t** 7.46min; **yield** 0.1%.

Coupling with tri(pentafluoro)phenylphosphine co-catalyst

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0559g, 0.307mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), $P(C_6F_5)_3$ (0.0133g, 0.0250mmol) and CsF (0.0888g, 0.585mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.47min; **yield** 0.3%.

Coupling with trimesitylphosphine co-catalyst

Tolylgermane **1** (0.0995g, 0.257mmol), 4-bromobenzonitrile (0.0586g, 0.322mmol), $Pd_2(dba)_3$ (0.0059g, 0.00644mmol), $P(2,4,6\text{-trimethylbenzene})_3$ (0.0100g, 0.0257mmol) and CsF (0.0818g, 0.539mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.45min; **yield** 0.1%.

Coupling with diphenyl-2-pyridylphosphine co-catalyst

Tolylgermane **1** (0.0989g, 0.256mmol), 4-bromobenzonitrile (0.0551g, 0.303mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), $PPh_2(2\text{-pyridyl})$ (0.0068g, 0.0258mmol) and CsF (0.0897g, 0.591mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.44min; **yield** trace.

Coupling with dppe co-catalyst

Tolylgermane **1** (0.0997g, 0.258mmol), 4-bromobenzonitrile (0.0567g, 0.311mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), dppe (0.0050g, 0.0125mmol) and CsF (0.0906g, 0.596mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.48min; **yield** 0.4%.

Coupling with dppp co-catalyst

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0575g, 0.316mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), dppp (0.0053g, 0.0128mmol) and CsF (0.110g, 0.724mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.50min; **yield** 1.1%.

Coupling with dppf co-catalyst

Tolylgermane **1** (0.0989g, 0.256mmol), 4-bromobenzonitrile (0.0550g, 0.302mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), dppf (0.0071g, 0.0128mmol) and CsF (0.0853g, 0.562mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.45min; **yield** 0.1%.

Coupling with binap co-catalyst

Tolylgermane **1** (0.102g, 0.264mmol), 4-bromobenzonitrile (0.0580g, 0.319mmol), $Pd_2(dba)_3$ (0.0060g, 0.00655mmol), Binap (0.0081g, 0.0130mmol) and CsF (0.0875g, 0.576mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.49min; **yield** 0.8%.

Coupling with dicyclohexyl(o-biphenyl)phosphine co-catalyst

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0571g, 0.314mmol), $Pd_2(dba)_3$ (0.0061g, 0.00666mmol), PCy_2(*o*-biphenyl) (0.0091g, 0.0260mmol) and CsF (0.0909g, 0.598mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.46min; **yield** trace.

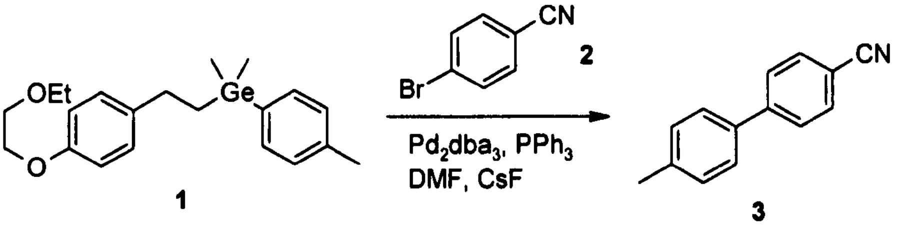
Coupling with tri-tert-butylphosphine co-catalyst

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0565g, 0.310mmol), Pd_2dba_3 (0.0059g, 0.00644mmol), $P(t\text{-}Bu)_3$ (1.168M in anhydrous THF, 22μL, 0.0257mmol) and CsF (0.0923g, 0.608mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.46min; **yield** trace.

Coupling with triethylphosphite co-catalyst

Tolylgermane **1** (0.103g, 0.266mmol), 4-bromobenzonitrile (0.0561g, 0.308mmol), Pd_2dba_3 (0.0060g, 0.00655mmol), $P(OEt)_3$ (4.4μL, 0.0042g, 0.0253mmol) and CsF (0.0894g, 0.589mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_t$** 7.45min; **yield** trace.

6.2.1.4 Cross-coupling: Experiments in an inert atmosphere (Figure 4.16)



Experiments in an inert atmosphere general method: Experiment 1

Tolylgermane **1** (0.0998g, 0.258mmol), 4-bromobenzonitrile (0.0551g, 0.303mmol), Pd_2dba_3 (0.0230g, 0.0251mmol), PPh_3 (0.0247g, 0.0942mmol), were dissolved in anhydrous DMF (1.5mL) in a round bottom flask fitted with a condenser and placed in an N_2 atmosphere. Anhydrous CsF (0.104g, 0.685mmol) was weighed under a stream of N_2 and then added to the reaction flask, which was again placed in an N_2 atmosphere. The mixture was then heated at 150°C.

After 1 hour a 25μL sample of crude reaction mixture was removed, naphthalene solution (10μL, 0.25M) was added and the mixture diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS indicated the presence of 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_t$** 7.46min; **yield** 1.3%.

After 24 hours a 25 μL sample of crude reaction mixture was removed, naphthalene solution (10 μL, 0.25M) was added and the mixture diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS indicated the presence of 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_t$** 7.46min; **yield** 1.3%.

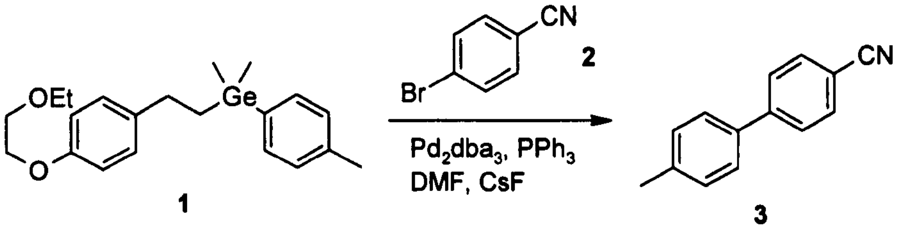
Experiment 2: Degassed reaction mixture

As for the general method for experiments in an inert atmosphere, except using tolylgermane **1** (0.105g, 0.271mmol), 4-bromobenzonitrile (0.0586g, 0.322mmol), Pd_2dba_3 (0.0246g, 0.0269mmol), PPh_3 (0.0270g, 0.103mmol), and CsF (0.0833g, 0.548mmol) dissolved in anhydrous DMF (1.5mL). The reaction mixture was subjected to three freeze-pump-thaw degassing cycles before being heated at 150°C.

After 1 hour analysis by quantitative GC/MS indicated the presence of 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.48min; **yield** 1.9%.

After 24 hours analysis by quantitative GC/MS indicated the presence of 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.47min; **yield** 1.9%.

6.2.1.5 Cross-coupling: Time-temperature investigation (Figure 4.17)



Tolylgermane **1** (0.102g, 0.264mmol), 4-bromobenzonitrile (0.0580g, 0.319mmol), Pd_2dba_3 (0.0237g, 0.0259mmol), PPh_3 (0.0269g, 0.103mmol), were dissolved in anhydrous DMF (1.5mL) in a round bottom flask fitted with a condenser and placed in an N_2 atmosphere. Anhydrous CsF (0.0830g, 0.546mmol) was weighed under a stream of N_2 and then added to the reaction flask, which was again placed in an N_2 atmosphere. The mixture was then heated at 80°C.

After 1 hour a 25μL sample of crude reaction mixture was removed, naphthalene solution (10μL, 0.25M) was added and the mixture diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS indicated the presence of 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.44min; **yield** trace.

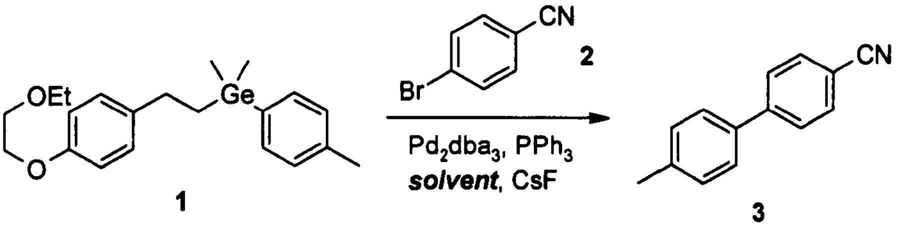
The reaction was further heated at 80°C for a second hour, before being sampled again. 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.44min; **yield** trace.

The temperature was then raised to 100°C, and the reaction sampled after a third hour. 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_t$** 7.44min; **yield** trace.

The temperature was finally raised to 120°C, and sampled after a fourth hour. 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_t$** 7.44min; **yield** 0.1%.

The reaction was heated at 120°C for 17 hours (21 hours in total), before being finally sampled. 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_t$** 7.44min; **yield** 0.1%.

6.2.1.6 Cross-coupling: Solvent screen (Figure 4.19)



General method

A 3mL reaction vial was charged with tolylgermane **16**, 4-bromobenzonitrile, $Pd_2(dba)_3$, PPh_3, and CsF. The reagents were dissolved in various solvents (1.5mL), sealed and heated at 150°C for 48 hours. Naphthalene solution (0.01mL, 0.25M) was added to a 25μL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS gave the following results.

Coupling with DMF solvent

Tolylgermane **1** (0.0896g, 0.231mmol), 4-bromobenzonitrile (0.0502g, 0.276mmol), Pd_2dba_3 (0.0211g, 0.0230mmol), PPh_3 (0.0244g, 0.0930mmol) and CsF (0.0797g, 0.525mmol) dissolved in anhydrous DMF (1.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_t$** 7.47min; **yield** 1.0%.

Coupling with DMA solvent

Tolylgermane **1** (0.0911g, 0.235mmol), 4-bromobenzonitrile (0.0509g, 0.280mmol), Pd_2dba_3 (0.0212g, 0.0232mmol), PPh_3 (0.0243g, 0.0926mmol) and CsF (0.0895g, 0.589mmol) dissolved in DMA (1.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_t$** 7.49min; **yield** 4%.

Coupling with NMP solvent

Tolylgermane **1** (0.0893g, 0.231mmol), 4-bromobenzonitrile (0.0506g, 0.278mmol), Pd_2dba_3 (0.0213g, 0.0233mmol), PPh_3 (0.0244g, 0.0930mmol) and CsF (0.0869g, 0.572mmol) dissolved in NMP (1.5mL). **GC/MS R*t*** 7.44min; **yield** trace.

Coupling with MeCN solvent

Tolylgermane **1** (0.0900g, 0.233mmol), 4-bromobenzonitrile (0.0514g, 0.282mmol), Pd_2dba_3 (0.0211g, 0.0230mmol), PPh_3 (0.0239g, 0.0911mmol) and CsF (0.0802g, 0.528mmol) dissolved in anhydrous MeCN (1.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R*t*** 7.44min; **yield** 0.1%.

Coupling with DMSO solvent

Tolylgermane **1** (0.0894g, 0.231mmol), 4-bromobenzonitrile (0.0506g, 0.278mmol), Pd_2dba_3 (0.0213g, 0.0233mmol), PPh_3 (0.0241g, 0.0919mmol) and CsF (0.0749g, 0.493mmol) dissolved in DMSO (1.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R*t*** 7.44min; **yield** trace.

Coupling with THF solvent

Tolylgermane **1** (0.0880g, 0.227mmol), 4-bromobenzonitrile (0.0490g, 0.269mmol), Pd_2dba_3 (0.0215g, 0.0235mmol), PPh_3 (0.0245g, 0.0934mmol) and CsF (0.0870g, 0.573mmol) dissolved in anhydrous THF (1.5mL). **GC/MS R*t*** 7.44min; **yield** 0.1%.

Coupling with 1,4-dioxane solvent

Tolylgermane **1** (0.0895g, 0.231mmol), 4-bromobenzonitrile (0.0503g, 0.276mmol), Pd_2dba_3 (0.0215g, 0.0235mmol), PPh_3 (0.0242g, 0.0923mmol) and CsF (0.1011g, 0.665mmol) dissolved in anhydrous 1,4-dioxane (1.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R*t*** 7.44min; **yield** trace.

Coupling with DME solvent

Tolylgermane **1** (0.0895g, 0.231mmol), 4-bromobenzonitrile (0.0501g, 0.275mmol), Pd_2dba_3 (0.0212g, 0.0232mmol), PPh_3 (0.0244g, 0.0930mmol) and CsF (0.1034g, 0.681mmol) dissolved in DME (1.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R*t*** 7.44min; **yield** 0.1%.

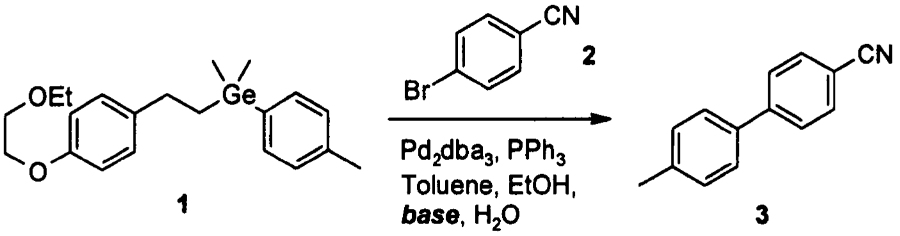
Coupling with toluene solvent

Tolylgermane **1** (0.0890g, 0.230mmol), 4-bromobenzonitrile (0.0501g, 0.275mmol), Pd_2dba_3 (0.0211g, 0.0230mmol), PPh_3 (0.0244g, 0.0930mmol) and CsF (0.0807g, 0.531mmol) dissolved in anhydrous toluene (1.5mL). **GC/MS R_f** 7.44min; **yield** trace.

Coupling with pyrrolidine solvent

Tolylgermane **1** (0.0993g, 0.257mmol), 4-bromobenzonitrile (0.0567g, 0.312mmol), Pd_2dba_3 (0.0237g, 0.0259mmol), and PPh_3 (0.0272g, 0.104mmol) dissolved in anhydrous DMF (1.5mL); 4-Cyano-4'-methyl-biphenyl was not observed.

6.2.1.7 Cross-coupling: Biphasic reactions (Figures 4.20 and 4.21)



Biphasic reaction general method: Coupling with KOH activator in toluene/water solvent system

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0570g, 0.313mmol), Pd_2dba_3 (0.0211g, 0.0230mmol), and PPh_3 (0.0243g, 0.0926mmol), were dissolved in anhydrous toluene (1mL), and anhydrous EtOH (0.2mL) in a round bottom flask. KOH (0.0353g, 0.628mmol) was dissolved in distilled water (0.5mL) and added to the organic solution and a condenser fitted. The reaction apparatus was evacuated and flushed with N_2 (×3), before being heated at 115°C for 17 hours.

Naphthalene solution (10μL, 0.25M) was added to a 25μL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution, which was then analysed by quantitative GC/MS to indicate the presence of 4-Cyano-4'-methyl-biphenyl; **GC/MS R_f** 7.45min; **yield** 0.3%.

Coupling with NaOAc activator in toluene/water solvent system

Tolylgermane **1** (0.0999g, 0.258mmol), 4-bromobenzonitrile (0.0561g, 0.308mmol), Pd_2dba_3 (0.0212g, 0.0232mmol), and PPh_3 (0.0244g, 0.0930mmol), and a solution of NaOAc (0.0465g, 0.567mmol) dissolved in distilled water (0.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.44min; **yield** trace.

Coupling with TBAF.3H_2O activator in toluene/water solvent system

Tolylgermane **1** (0.102g, 0.264mmol), 4-bromobenzonitrile (0.0587g, 0.322mmol), Pd_2dba_3 (0.0212g, 0.0232mmol), PPh_3 (0.0243g, 0.0926mmol), and a solution of TBAF.3H_2O (0.190g, 0.603mmol) dissolved in distilled water (0.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.44min; **yield** trace.

Coupling with KOH activator and $Pd(PPh_3)_4$ catalyst in toluene/water solvent system

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0570g, 0.313mmol), $Pd(PPh_3)_4$ (0.0596g, 0.0515mmol), and a solution of KOH (0.0353g, 0.628mmol) dissolved in distilled water (0.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.45min; **yield** 0.1%.

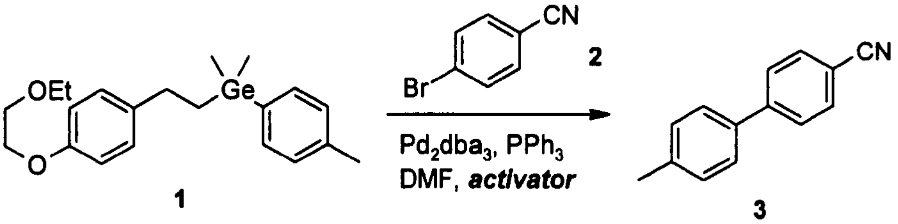
Coupling with degassed aqueous KOH activator in toluene/water solvent system

Tolylgermane **1** (0.102g, 0.264mmol), 4-bromobenzonitrile (0.0573g, 0.315mmol), Pd_2dba_3 (0.0234g, 0.0256mmol), and PPh_3 (0.0268g, 0.102mmol). KOH (0.0975g, 0.174mmol) was dissolved in distilled water (1mL) and the resulting solution degassed with 3 freeze-pump-thaw cycles. 0.35mL of this solution was added to the reaction mixture. 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.45min; **yield** trace.

Coupling with degassed aqueous CsF activator in toluene/water solvent system

Tolylgermane **1** (0.0992g, 0.256mmol), 4-bromobenzonitrile (0.0578g, 0.318mmol), Pd_2dba_3 (0.0238g, 0.0260mmol), and PPh_3 (0.0274g, 0.104mmol). CsF (0.262g, 0.173mmol) was dissolved in distilled water (1mL) and the resulting solution degassed with 3 freeze-pump-thaw cycles. 0.35mL of this solution was added to the reaction mixture. **GC/MS R_t** 7.45min; **yield** trace.

6.2.1.8 Cross-coupling: Activator screen (Figure 4.22)



General method

A 3mL reaction vial was charged with tolylgermane **16**, 4-bromobenzonitrile, $Pd_2(dba)_3$, PPh_3, and various activators. The reagents were dissolved DMF (1.5mL), sealed and heated at 150°C for 48 hours. Naphthalene solution (0.01mL, 0.25M) was added to a 25μL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS gave the following results.

Coupling with DMAP activator

Tolylgermane **1** (0.0995g, 0.257mmol), 4-bromobenzonitrile (0.0572g, 0.314mmol), Pd_2dba_3 (0.0229g, 0.0250mmol), PPh_3 (0.0238g, 0.0907mmol) and DMAP (0.0712g, 0.583mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.47min; **yield** 0.2%.

Coupling with NaOMe activator

Tolylgermane **1** (0.0993g, 0.257mmol), 4-bromobenzonitrile (0.0568g, 0.312mmol), Pd_2dba_3 (0.0212g, 0.0232mmol), PPh_3 (0.0245g, 0.0934mmol) and commercial NaOMe (0.0334g, 0.618mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.47min; **yield** 0.1%.

Coupling with CsOH activator

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0554g, 0.304mmol), Pd_2dba_3 (0.0216g, 0.0236mmol), PPh_3 (0.0245g, 0.0934mmol) and CsOH (0.0938g, 0.795mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.44min; **yield** trace.

Coupling with DABCO activator

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0568g, 0.312mmol), Pd_2dba_3 (0.0215g, 0.0235mmol), PPh_3 (0.0241g, 0.0919mmol) and DABCO (0.0678g, 0.605mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_f$** 7.44min; **yield** trace.

Coupling with pyrrolidine activator

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0571g, 0.314mmol), Pd_2dba_3 (0.0235g, 0.0257mmol), PPh_3 (0.0273g, 0.104mmol) and pyrrolidine (47μL, 0.0402g, 0.566mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_f$** 7.41min; **yield** 0.1%.

Coupling with hydroxylamine activator

Tolylgermane **1** (0.0998g, 0.258mmol), 4-bromobenzonitrile (0.0561g, 0.308mmol), Pd_2dba_3 (0.0235g, 0.0257mmol), PPh_3 (0.0268g, 0.102mmol), $H_2N\text{-}OH.HCl$ (0.0400g, 0.576mmol), and NEt_3 (0.08mL, 0.0581g, 0.574mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_f$** 7.41min; **yield** 0.1%.

Coupling with anionic peroxide activator

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0573g, 0.315mmol), Pd_2dba_3 (0.0236g, 0.0258mmol), PPh_3 (0.0268g, 0.102mmol), H_2O_2 (aqueous 6%w/v, 0.325mL, 0.573mmol), and $LiOH.H_2O$ (0.0242g, 0.577mmol). 4-Cyano-4'-methyl-biphenyl was not observed.

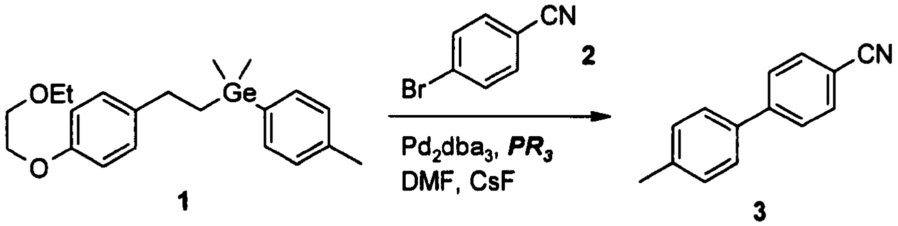
Coupling with silver(I) oxide activator

Tolylgermane **1** (0.0999g, 0.258mmol), 4-iodobenzonitrile (0.0716g, 0.313mmol), Pd_2dba_3 (0.0238g, 0.0260mmol), PPh_3 (0.0270g, 0.103mmol) and Ag_2O (0.0732g, 0.316mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_f$** 7.42min; **yield** 0.1%.

Coupling without activator

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0567g, 0.311mmol), Pd_2dba_3 (0.0235g, 0.0256mmol), and PPh_3 (0.0270g, 0.103mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R$_f$** 7.44min; **yield** 0.5%.

6.2.1.9 Cross-coupling: Phosphine screen in the absence of activator (Figure 4.23)



General method

A 3mL reaction vial was charged with tolylgermane **16**, 4-bromobenzonitrile, $Pd_2(dba)_3$, and various phosphines. The reagents were dissolved in DMF (1.5mL), sealed and heated at 150°C for 48 hours. Naphthalene solution (0.01mL, 0.25M) was added to a 25µL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS gave the following results.

Coupling with triphenylphosphine co-catalyst

Tolylgermane **1** (0.0996g, 0.257mmol), 4-bromobenzonitrile (0.0570g, 0.313mmol), Pd_2dba_3 (0.0238g, 0.0260mmol), and PPh_3 (0.0271g, 0.103mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R*t*** 7.43min; **yield** 0.4%.

Coupling with tri-(4-fluorophenyl)phosphine co-catalyst

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0570g, 0.313mmol), Pd_2dba_3 (0.0236g, 0.0258mmol), and $P(p\text{-}C_6H_4F)_3$ (0.0326g, 0.103mmol); 4-Cyano-4'-methyl-biphenyl; **GC/MS R*t*** 7.43min; **yield** 0.9%.

Coupling with tri(pentafluoro)phenylphosphine co-catalyst

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0569g, 0.313mmol), Pd_2dba_3 (0.0235g, 0.0257mmol), and $P(C_6F_5)_3$ (0.0539g, 0.101mmol). 4-Cyano-4'-methyl-biphenyl was not observed.

Coupling with dppp co-catalyst

Tolylgermane **1** (0.0995g, 0.257mmol), 4-bromobenzonitrile (0.0561g, 0.308mmol), Pd_2dba_3 (0.0236g, 0.0258mmol), and dppp (0.0213g, 0.0516mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R*t*** 7.44min; **yield** 0.8%.

Coupling with dppe co-catalyst

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0568g, 0.312mmol), Pd_2dba_3 (0.0237g, 0.0259mmol), and dppe (0.0205g, 0.0515mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_f** 7.43min; **yield** 0.3%.

Coupling with Binap co-catalyst

Tolylgermane **1** (0.0998g, 0.258mmol), 4-bromobenzonitrile (0.0569g, 0.313mmol), Pd_2dba_3 (0.0236g, 0.0258mmol), and binap (0.0317g, 0.0509mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_f** 7.46min; **yield** 3%.

Coupling with triphenylphosphine co-catalyst and DMA solvent

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0571g, 0.314mmol), Pd_2dba_3 (0.0239g, 0.0261mmol), and PPh_3 (0.0269g, 0.103mmol) dissolved in DMA (1.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_f** 7.42; **yield** 0.5%.

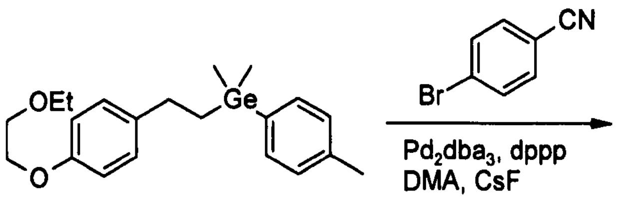
Coupling with less than stoichiometric amount activator

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0568g, 0.312mmol), Pd_2dba_3 (0.0236g, 0.0258mmol), PPh_3 (0.0269g, 0.103mmol) and CsF (0.0092g, 0.0606mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_f** 7.43min; **yield** 1.5%.

Unactivated coupling with anisylgermane

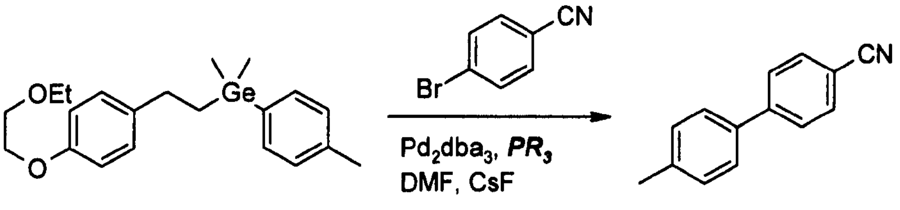
Anisylgermane **13** (0.104g, 0.258mmol), 4-bromobenzonitrile (0.0570g, 0.313mmol), Pd_2dba_3 (0.0236g, 0.0258mmol), and PPh_3 (0.0269g, 0.103mmol); 4-Cyano-4'-methoxy-biphenyl **GC/MS R_f** 10.17min; **yield** 3%.

6.2.1.10 Best case coupling (Figure 4.24)



Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0570g, 0.313mmol), Pd_2dba_3 (0.0235g, 0.0257mmol), dppp (0.0207g, 0.502mmol) and CsF (0.0895g, 0.589mmol) dissolved in DMA (1.5mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 7.45min; **yield** 4%.

6.2.1.11 Cross-coupling: Second phosphine screen (Figure 4.55)



General method

The reactions were carried out using the general method for the previous phosphine screen (*vide supra*). The reagents were dissolved in 1.35mL of anhydrous DMF

Coupling with triphenylphosphine co-catalyst

Tolylgermane **1** (0.0907g, 0.234mmol), 4-bromobenzonitrile (0.0514g, 0.282mmol), Pd_2dba_3 (0.0105g, 0.0115mmol), PPh_3 (0.0122g, 0.0465mmol) and CsF (0.155g, 1.02mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 8.67min; **yield** 3%.

Coupling with tri-(4-fluorophenyl)phosphine co-catalyst

Tolylgermane **1** (0.0887g, 0.229mmol), 4-bromobenzonitrile (0.0508g, 0.279mmol), Pd_2dba_3 (0.0106g, 0.0116mmol), $P(p\text{-}C_6H_4F)_3$ (0.0147g, 0.0465mmol) and CsF (0.0808g, 0.532mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 8.67min; **yield** 3%.

Coupling with tri(pentafluoro)phenylphosphine co-catalyst

Tolylgermane **1** (0.0896g, 0.232mmol), 4-bromobenzonitrile (0.0512g, 0.281mmol), Pd_2dba_3 (0.0106g, 0.0116mmol), $P(C_6F_5)_3$ (0.0249g, 0.0468mmol) and CsF (0.0739g, 0.487mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 8.68min; **yield** 7%.

Coupling with dppp co-catalyst

Tolylgermane **1** (0.0889g, 0.230mmol), 4-bromobenzonitrile (0.0511g, 0.281mmol), Pd_2dba_3 (0.0106g, 0.0116mmol), dppp (0.0095g, 0.0230mmol) and CsF (0.0743g, 0.489mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R_t** 8.67min; **yield** 2%.

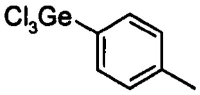
Coupling with binap co-catalyst

Tolylgermane **1** (0.0892g, 0.230mmol), 4-bromobenzonitrile (0.0517g, 0.284mmol), Pd_2dba_3 (0.0104g, 0.0114mmol), binap (0.0141g, 0.0226mmol) and CsF (0.0823g, 0.541mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS R*t*** 8.67min; **yield** 6%.

6.2.2 Approaches towards chlorogermane cross-coupling

6.2.2.1 Synthesis of chlorogermanes

(4-Methyl-phenyl)trichlorogermane (44)[187]



44

Molecular Weight =270.08
Molecular Formula =$C_7H_7Cl_3Ge$

Method 1

According to the method of Schmidbaur,[187] 4-bromotoluene (17.3g, 0.101mol), $GeCl_2 \cdot 1,4$-dioxane **7** (synthesised *via* reduction with TMDS, 0.506g, 2.18mmol), and aluminium(III) chloride (0.0299g, 0.244mmol) were combined, placed under N_2 and heated at 80°C for 25 hours. The hot mixture was then filtered through a hot sinter, and the resulting solids washed with hot anhydrous toluene. Solvent was removed from the filtrate *in vacuo*, and the resulting sample was further purified by reduced pressure distillation to remove 4-bromotoluene. NMR analysis of the distillation residue indicated that there was none of the desired product present.

Method 2: Sealed tube

$GeCl_2 \cdot 1,4$-dioxane **7** (synthesised *via* reduction with TMDS, 0.495g, 2.14mmol), 4-bromotoluene (3.63g, 21.2mmol), aluminium(III) chloride (0.0360g, 0.270mmol) and anhydrous 1,4-dioxane (1mL) were combined in a sealed tube and heated at 140°C for 44 hours. The mixture was allowed to cool and then diluted with $CHCl_3$ (10mL) before being filtered. Solvent was removed from the filtrate *in vacuo* to give a cream solid (3.14g). GC/MS of the crude reaction mixture revealed a large amount of starting bromotoluene, and only a trace of the desired product **44**:

4-Bromotoluene[220] **R_f** 0.87 (petrol/EtOAc, 9/1); **^1H NMR** ($CDCl_3$) δ 2.31 (3H, s, ArCH_3), 7.06 (2H, d, *J* 8.5, BrCCHC*H*CCH_3), 7.38 (2H, d, *J* 8.5, BrCC*H*CHCCH_3); **GC/MS R_t** 5.42min; **MS** (EI) *m/z* 170 (37%, M^{+}), 91 (100%), 65 (24%).

Trichlorotolylgermane[187] **44**. **R_f** 0.00 (petrol/EtOAc, 9/1); **GC/MS R_t** 9.73 min; **MS** (EI) *m/z* 270 (16%, M^{+}), 235 (20%), 126 (38%), 91 (100%), 65 (38%).

Method 3

According to the method of Schmidbaur,[187] 4-bromotoluene (0.696g, 4.07mmol), $GeCl_2 \cdot 1,4$-dioxane **7** (synthesised *via* reduction with Et_3SiH, 0.021g, 0.0885mmol), and aluminium(III) chloride (1mg, 9μmol) were combined, placed under N_2 and heated at 80°C for 24 hours. The crude sample was dissolved in CH_2Cl_2 (10mL) and filtered to remove solids. Solvent was removed from the filtrate *in vacuo* and the sample then distilled under reduced pressure to leave a viscous oil (8mg). Analysis by GC/MS revealed the presence of 4-bromotoluene as the major component, with the desired products trace amounts:

4-Bromotoluene. Analytical data as above.

Trichlorotolylgermane **44**. Analytical data as above.

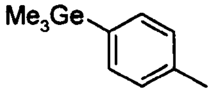
Tribromotolylgermane[187] **45**: **R_f** 0.00 (petrol/EtOAc, 9/1); **GC/MS R_t** 12.94 min; **MS** (EI) *m/z* 402 (6%, M^{+}), 321 (34%), 279 (4%), 234 (4%), 153 (45%), 91 (100%), 65 (87%).

Germanium(IV) ethoxide (46)[191]

$Ge(OEt)_4$ Molecular Weight =252.84
46 Molecular Formula =$C_8H_{20}GeO_4$

Sodium metal (0.972g, 42.2mmol) was added to anhydrous ethanol (20mL) and then flushed with N_2. The resulting suspension was stirred at rt until the sodium had dissolved. Germanium(IV) chloride **6** (1mL, 1.88g, 8.76mmol) was then added dropwise to the solution of sodium ethoxide and the solution refluxed for 3 hours. The reaction mixture was then centrifuged at 3200rpm for 10 minutes, the supernatant was decanted and solvent removed *in vacuo*. The resulting residue was purified by Kugelrohr distillation under N_2, collecting the fraction boiling between 183-189°C to give germanium(IV) ethoxide **46** as a clear colourless liquid (0.594g, 2.35mmol, 27%), **R*f*** 0.00 (petrol/EtOAc, 9/1); **^{1}H NMR** (CDCl$_3$) δ 1.28 (12H, t, *J* 7.0, OCH_2CH_3), 3.96 (8H, q, *J* 7.0, OCH_2CH_3); **IR** (neat) 3328, 2973, 1380, 1090, 1049, 881cm^{-1}.

(4-methyl-phenyl)trimethylgermane (41)[221]



41

Molecular Weight =208.83
Molecular Formula =$C_{10}H_{16}Ge$

Method 1: Reaction of germanium(IV) chloride with 4-methyl-phenyl magnesium bromide

Germanium(IV) chloride **6** (85µL, 0.160g, 0.750mmol) was dissolved in anhydrous THF (10mL), and cooled to -78°C. A solution of 4-methyl-phenyl magnesium bromide (1.0M in THF, 0.75mL, 0.750mmol) was then added both dropwise and slowly and the mixture stirred for 1 hour. A solution of methyl magnesium bromide (3.0M in Et_2O, 1.5mL, 4.5mmol) was then added dropwise and the solution allowed to warm to rt, before being refluxed for 1 hour. Distilled water (1mL) was added dropwise to destroy excess Grignard reagent, aqueous HCl (1.0M, 5mL) was added, and the solution extracted with Et_2O (2 × 10mL). Organic washings were combined and dried with $MgSO_4$ before being filtered and concentrated *in vacuo* to give 0.142g of crude reaction products. GC/MS analysis of the crude mixture revealed a complex reaction mixture including:

4-Bromotoluene. Analytical data as above

Tolyltrimethylgermane[221] 41: **R*f*** 0.84 (Petrol/EtOAc, 9/1); **GC/MS R*t*** 6.62min; **MS** (EI) *m/z* 210 (M^{+} 6%), 195(100%), 165(19%), 91(32%).

4,4'-Dimethyl-biphenyl[222]: **R*f*** 0.91 (Petrol/EtOAc, 9/1); **GC/MS R*t*** 12.44min; **MS** (EI) *m/z* 182 (M^{+} 100%), 167 (56%), 89 (18%).

A compound tentatively assigned as ***ditolyldimethylgermane***[223] **47**: **R*f*** 0.84 (Petrol/EtOAc, 9/1); **GC/MS R*t*** 14.80min; **MS** (EI) *m/z* 286 (M^{+} 3%), 271 (100%), 165 (27%), 91 (33%).

A compound tentatively assigned as ***tritolylmethylgermane***: **R*f*** 0.84 (Petrol/EtOAc, 9/1); **GC/MS R*t*** 20.72min; **MS** (EI) *m/z* 362 (M^{+} 1%), 347 (100%), 271 (13%), 165 (50%), 91 (52%).

Tolyltrimethylgermane **41**/ditolyldimethylgermane **47** were present in 87/13 ratio from ^{1}H NMR, integrating diagnostic germanium methyl peaks at δ 0.40ppm and δ 0.64ppm respectively.

Method 2: Reaction of germanium(IV) ethoxide with 4-methyl-phenyl magnesium bromide

Germanium(IV) ethoxide **46** (0.198g, 0.783mmol) was dissolved in anhydrous THF (10mL), and cooled to -78°C. A solution of 4-methyl-phenyl magnesium bromide (1.0M in THF, 0.75mL, 0.750mmol) was then added both dropwise and slowly and the mixture stirred for 1 hour. A solution of methyl magnesium bromide (3.0M in Et_2O, 1.5mL, 4.5mmol) was then added dropwise and the solution allowed to warm up to rt, before being refluxed for 1 hour. Distilled water (1mL) was added dropwise to destroy excess Grignard reagent, aqueous HCl (1.0M, 5mL) was added, and the solution extracted with Et_2O (2 × 10mL). Organic washings were combined and dried with $MgSO_4$ before being filtered and concentrated *in vacuo* to give 0.134g of crude reaction products. GC/MS analysis of the crude mixture revealed a complex reaction mixture including:

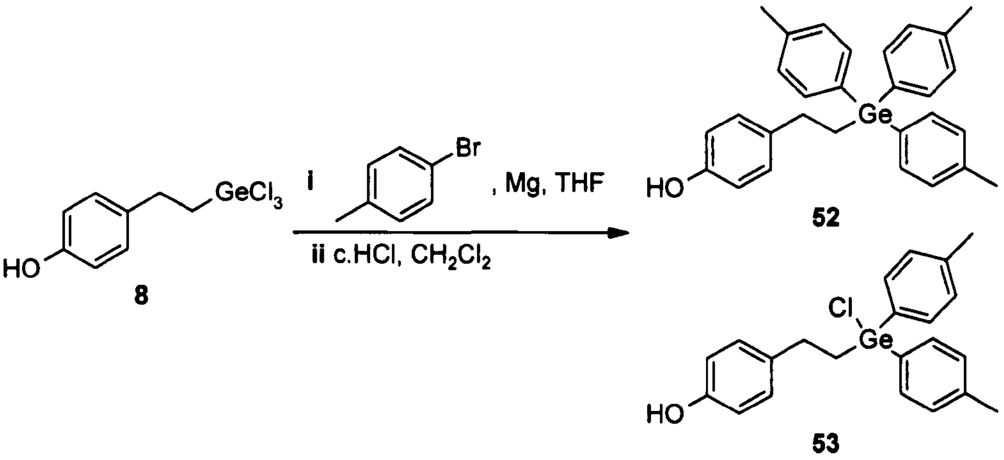
Tolyltrimethylgermane **41**. Analytical data as above.

4,4'-Dimethyl-biphenyl. Analytical data as above.

A compound tentatively assigned as ***ditolyldimethylgermane*** **47**. Analytical data as above.

Tolyltrimethylgermane **41**/ditolyldimethylgermane **47** were present in 82/18 ratio from ^{1}H NMR, integrating diagnostic germanium methyl peaks at δ 0.40 and δ 0.64 respectively.

Attempted synthesis of 4-{2-[dichloro-(4-methylphenyl)germanyl]ethyl} phenol (51)



4-Bromotoluene (40.8g, 0.239mol) was added to dry magnesium turnings (5.38g, 0.222mol) suspended in anhydrous THF (200mL) and the mixture stirred for 3 hours. The solution was decanted to remove precipitates and solids and then titrated using the method of Paquette[224] to give the concentration of the resulting Grignard reagent as 0.82mol dm^{-3}.

The Grignard reagent (115mL, 94.3mmol) was added to trichlorogermylphenol **8** (2.74g, 9.1mmol) dissolved in anhydrous THF (20mL), and the mixture then heated at reflux for 17 hours. Minimum distilled water was added dropwise to destroy excess Grignard reagent, solvents were then removed *in vacuo*. The residue was taken up in CH_2Cl_2 (70mL) and aqueous HCl (1M, 35mL) added dropwise over 90 min. The layers were separated and HCl (1M, 25mL) added to the CH_2Cl_2 layer, followed by c.HCl (150mL) with vigorous stirring for 1 hour. The acidified CH_2Cl_2 layer was then separated and the acid layer extracted with CH_2Cl_2 (2 × 100mL), organics were dried with $MgSO_4$, filtered, concentrated and analysed by ^{1}H NMR to give 8.17g of crude product including:

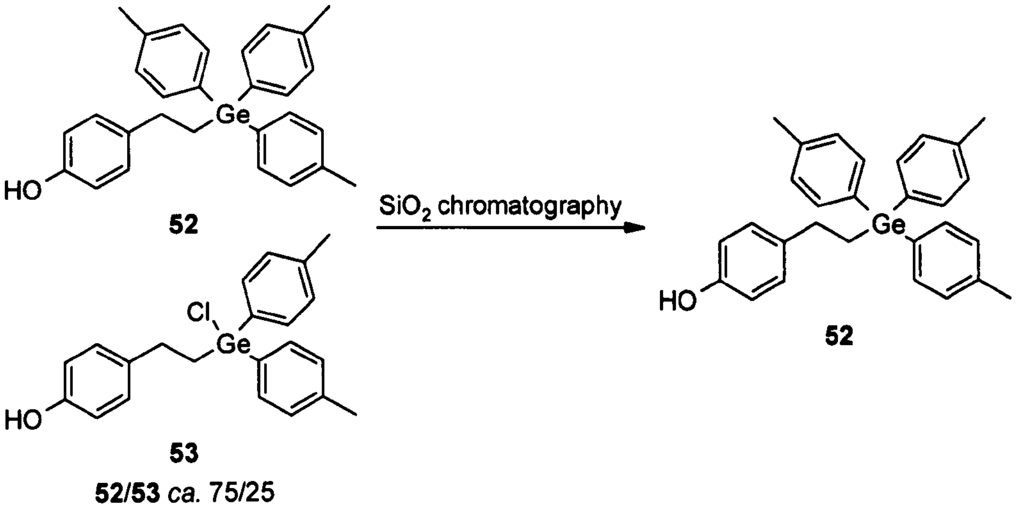
Tritolylgermylphenol **52**. Analytical data as below.

Chloroditolylphenol **53**. Analytical data as below.

Integration of the methylene signals α to germanium indicated that tritolylgermylphenol **52** (δ 2.77) and chloroditolylphenol **53** (δ 2.84) were present in a *ca.* 75/25 ratio by ^{1}H NMR.

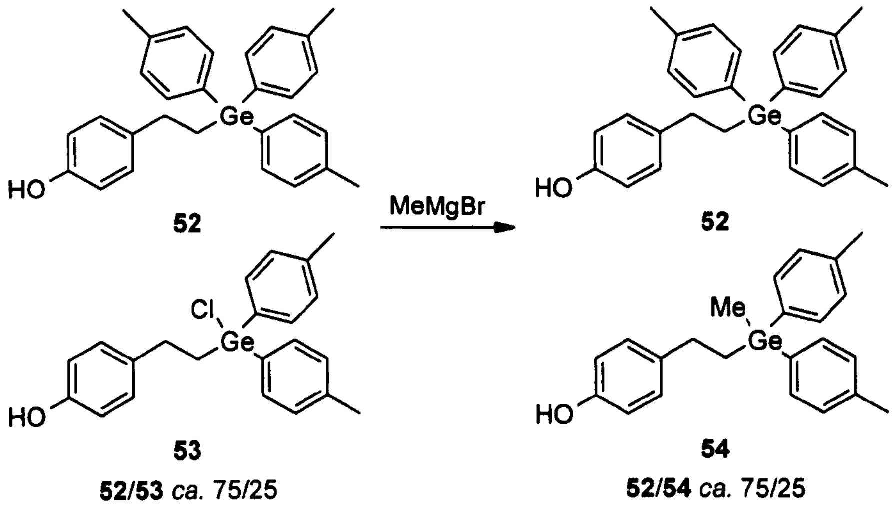
The crude mixture was then subjected to the following conditions:

Silica column chromatography



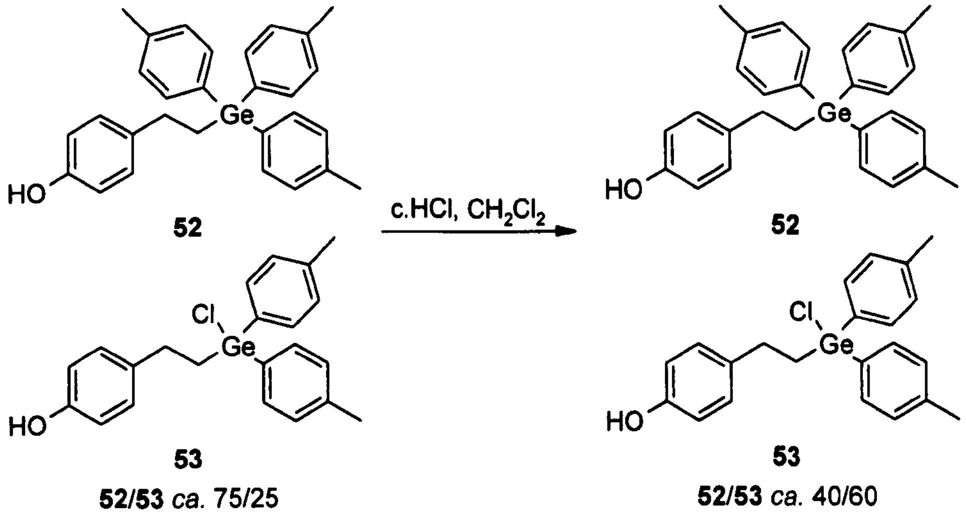
1.62g of the crude reaction mixture of **52** and **53** (*ca.* 75/25) was purified by column chromatography (10 × 5cm Silica gel, eluted with petrol/CH_2Cl_2 2/8) to give tritolylgermylphenol **52** (0.4569g, 0.978mmol). Analytical data as below.

Treatment with MeMgBr



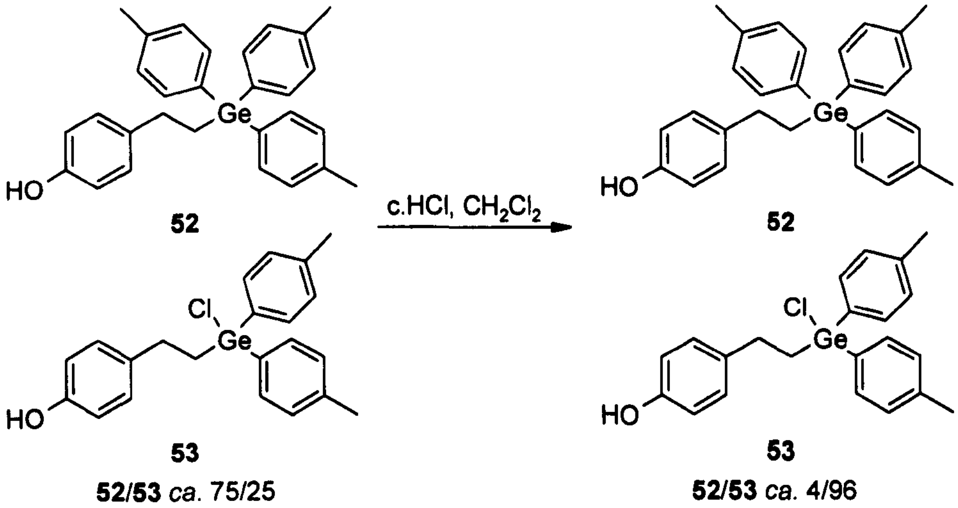
2.02g of the crude mixture of **52** and **53** (*ca.* 75/25) was dissolved in anhydrous toluene (35mL), and subjected to MeMgBr (3.0M in Et_2O, 3.8mL, 11.4mmol) at 115°C for 17 hours. Water was added dropwise to destroy excess Grignard reagent and the resulting mixture partitioned between CH_2Cl_2 (3 × 50mL) and aqueous HCl (1M, 30mL). Organics were dried with $MgSO_4$, filtered and concentrated *in vacuo* and analysed by ^1H NMR as before to give tritolylgermylphenol **52** and methylditolylphenol **54** in a *ca.* 75/25 ratio.

Treatment with c.HCl at 30°C



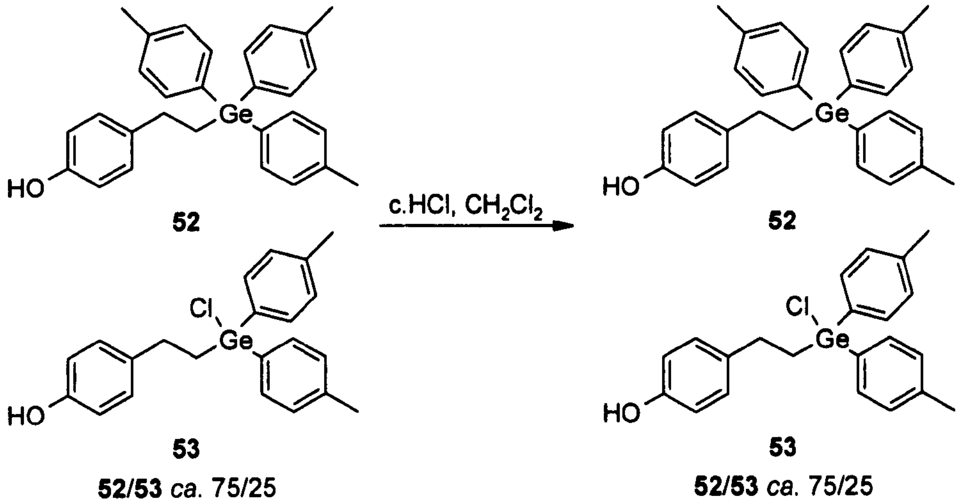
2.50g of crude mixture of **52** and **53** (*ca.* 75/25) were dissolved in CH_2Cl_2 (15mL), c.HCl (40mL) was added, and the biphasic mixture heated at 30°C for 23 hours. The layers were separated, and the acid extracted with CH_2Cl_2 (3 × 70mL), organics combined, dried with $MgSO_4$, concentrated *in vacuo* and analysed by ^1H NMR as before to give tritolylgermylphenol **52** and chloroditolylphenol **53** in a *ca.* 40/60 ratio by ^1H NMR.

Treatment with c.HCl at 40°C



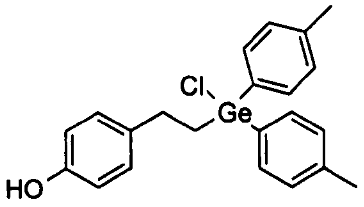
1.01g of crude mixture of **52** and **53** (*ca.* 75/25) were dissolved in CH_2Cl_2 (7mL) and c.HCl (40mL), and then heated at 40°C for 5 hours with vigorous stirring. The layers were separated, and the acid layer extracted with CH_2Cl_2 (2 × 30mL), organics were combined, dried with $MgSO_4$, filtered, concentrated and analysed by ^1H NMR as before to give tritolylgermylphenol **52** and chloroditolylphenol **53** in a *ca.* 4/96 ratio by ^1H NMR.

Treatment with acetic acid



1.02g of crude mixture of **52** and **53** (*ca.* 75/25) was dissolved in glacial acetic acid (20mL) and heated at 98°C for 5 hours. No consumption of starting material was observed by TLC (petrol/EtOAc, 9/1).

4-{2-[Chlorodi-(4-methylphenyl)germanyl]ethyl}phenol (53)

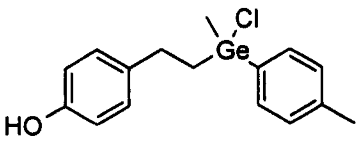


53

Molecular Weight =411.47
Molecular Formula =$C_{22}H_{23}ClGeO$

A solution of MSA (38μL, 0.0561g, 0.584mmol) in CH_2Cl_2 (1.46mL) was added to a solution of tritolylgermylphenol **52** (0.0502g, 0.107mmol) dissolved in CH_2Cl_2 (1mL) to give a solution with a concentration of MSA of 0.23M. The resulting mixture was stirred at rt for 35 minutes, before being neutralised with saturated $NaHCO_3$ solution until effervescence ceased. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 15mL), organics were combined and then shaken with c.HCl (20mL), separated again, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give chloroditolylphenol **53** as a brown oil (0.395g, 0.106mmol, 99%). $\mathbf{R}_f$ 0.00 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 1.90 (2H, m, $CH_2C\mathit{H}_2Ge$), 2.38 (6H, s, ArC*H*$_3$), 2.84 (2H, m, C*H*$_2$CH$_2$Ge), 5.29 (1H, s, OH), 6.72 (2H, d, *J* 8.5, HOCC*H*CHC), 7.05 (2H, d, *J* 8.5, HOCCHC*H*C), 7.24 (4H, d, *J* 8.0, GeCCHC*H*CCH$_3$), 7.47 (4H, d, *J* 8.0, GeCC*H*CHCCH$_3$); ^{13}**C NMR** (CDCl$_3$) δ 21.1 (t), 21.5 (q), 29.1 (t), 115.3 (d), 129.1 (d), 129.4 (d), 132.3 (s), 133.5 (d), 135.5 (s), 140.4 (s), 153.8 (s); **IR** (neat) 3368, 2920, 1598, 1515, 1234, 1090, 799, 595 cm^{-1}; **MS** (EI) *m/z* 412 (M^{+} 28%), 320 (11%), 291 (58%), 165 (14%), 120 (100%), 91 (45%); **HRMS** calc'd for $C_{22}H_{23}Cl^{74}GeO$ 412.0649, found 412.0667, error –4.3ppm.

4-{2-[Chloromethyl-(4-methylphenyl)germanyl]ethyl}phenol (55)

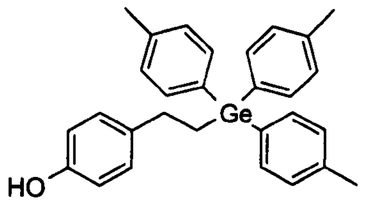


55

Molecular Weight =355.79
Molecular Formula =$C_{15}H_{16}Cl_2GeO$

A solution of MSA in CH$_2$Cl$_2$ (0.238M, 20mL) was added to methylditolylphenol **54** (0.459g, 1.17mmol) and the mixture stirred for 30 minutes before being neutralised with saturated aqueous NaHCO$_3$. The aqueous layer was then extracted with CH$_2$Cl$_2$ (2 × 20mL), the organic washings were combined and then treated with c.HCl (30mL), the phases were separated and the acid layer further extracted with CH$_2$Cl$_2$ (2 × 20mL). The organic washings were combined and dried with MgSO$_4$, before being filtered and concentrated *in vacuo* to give chloromethyltolylphenol **55** as a pale brown oil (0.318g, 0.947mmol, 99%). **R*f*** 0.00 (petrol/EtOAc, 9/1); ^{1}**H NMR** (CDCl$_3$) δ 0.80 (3H, s, GeC*H*$_3$) 1.70 (2H, m, CH$_2$C*H*$_2$Ge), 2.39 (3H, s, ArC*H*$_3$), 2.82 (2H, m, C*H*$_2$CH$_2$Ge), 6.76 (2H, d, *J* 8.5, HOCC*H*CHC), 7.06 (2H, d, *J* 8.5, HOCCHC*H*C), 7.25 (2H, d, *J* 8.0, GeCCHC*H*CCH$_3$), 7.45 (2H, d, *J* 8.0, GeCC*H*CHCCH$_3$), phenol proton not observed; ^{13}**C NMR** (CDCl$_3$) δ 1.7 (q), 21.5 (q), 22.4 (t), 29.1 (t), 115.3 (d), 129.1 (d), 129.3 (d), 132.6 (d), 145.1 (s), 150.8 (s), two quaternary carbons not seen; **IR** (neat) 3412, 3017, 2921, 1598, 1513, 1447, 1191, 1090, 797cm^{-1}; **MS** (EI) *m/z* 336 (M^{+} 3%), 244 (10%), 215 (34%), 201 (5%), 181 (5%), 165 (5%), 120 (100%), 91 (29%); **HRMS** calc'd for $C_{16}H_{19}Cl^{74}GeO$ 336.0336, found 336.0333, error 0.9ppm.

4-{2-[Tri-(4-methylphenyl)germanyl]ethyl}phenol (52)

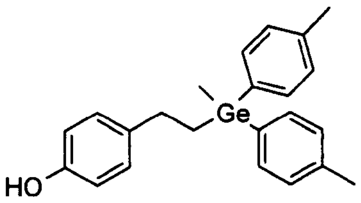


52

Molecular Weight =467.15
Molecular Formula =$C_{29}H_{30}GeO$

4-Bromotoluene (13.6g, 79.6mmol) dissolved in anhydrous THF (10mL) was added to a suspension of magnesium turnings (1.99g, 82.0mmol) in anhydrous THF (60mL). The solution was briefly warmed by hand to initiate the reaction and then allowed to stir for 1 hour at rt. Trichlorogermylphenol **8** (2.02g, 6.7mmol) was dissolved in anhydrous THF (10mL) and then added to the solution of Grignard reagent, the resulting mixture was refluxed for 22 hours. Distilled water was carefully added dropwise to destroy excess Grignard and aqueous HCl (1.0M, 75mL) was added to dissolve inorganics. The solution was then extracted with Et_2O (3 × 70mL) after which the organic washings were combined, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (8 × 10cm silica gel, eluted with petrol/EtOAc, 19/1 → petrol/EtOAc, 9/1) to give tritolylgermylphenol **52** as a clear colourless oil (2.48g, 5.31mmol, 79%). **R*f*** 0.42 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 1.80 (2H, m, CH_2CH_2Ge), 2.39 (9H, s, $ArCH_3$), 2.77 (2H, m, CH_2CH_2Ge), 4.69 (1H, s, O*H*), 6.74 (2H, d, *J* 8.5, HOCC*H*CHC), 7.07 (2H, d, *J* 8.5, HOCCHC*H*C), 7.22 (6H, d, *J* 8.0, GeCCHC*H*CCH$_3$), 7.41 (6H, d, *J* 8.0, GeCC*H*CHCCH$_3$); **^{13}C NMR** ($CDCl_3$) δ 16.4 (t), 21.5 (q), 30.3 (t), 115.1 (d), 118.8 (d), 129.1 (d), 133.5 (s), 134.9 (d), 137.2 (s), 138.7 (s), 153.5 (s); **IR** (neat) 3402, 2920, 1512, 1228, 1087, 799 cm^{-1}; **MS** (EI) *m/z* 468 (M^{+} 2%), 376 (19%), 347 (100%), 255 (10%), 181 (17%), 165 (21%), 91 (32%); **HRMS** calc'd for $C_{29}H_{30}{}^{74}GeO$ 468.1509, found 468.1518, error –2.0ppm; **Elemental analysis** expected for $C_{29}H_{30}GeO$ C 74.56%, H 6.47%, analysis found C 74.20%, H 6.55%..

4-{2-[Methyldi-(4-methylphenyl)germanyl]ethyl}phenol (54)

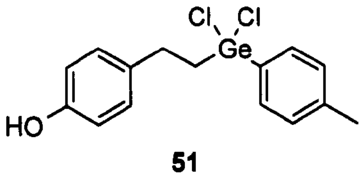


54

Molecular Weight =391.05
Molecular Formula =$C_{23}H_{26}GeO$

Methyl magnesium bromide (3.0M in Et_2O, 2mL, 6mmol) was added to a solution of chloroditolylphenol **53** (0.457g, 1.11mmol) in anhydrous toluene (10mL), and the resulting mixture heated at 115°C for 18 hours. Distilled water was added dropwise to destroy excess Grignard reagent, and the mixture then partitioned between Et_2O (100mL) and aqueous HCl (1M, 25mL), with the aqueous layer being further extracted with Et_2O (3 × 50mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give methylditolylphenol **54** as a pale brown oil (0.391g, 1.00mmol, 90%). **R$_f$** 0.66 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 0.60 (3H, s, GeCH$_3$), 1.53 (2H, m, CH$_2$C*H*$_2$Ge), 2.37 (6H, s, ArCH$_3$), 2.69 (2H, m, CH$_2$CH$_2$Ge), 4.57 (1H, bs, O*H*), 6.74 (2H, d, *J* 8.5, HOCC*H*CHC), 7.05 (2H, d, *J* 8.5, HOCCHC*H*C), 7.19 (4H, d, *J* 8.0, GeCCHC*H*CCH$_3$), 7.38 (4H, d, *J* 8.0, GeCC*H*CHCCH$_3$); **^{13}C NMR** ($CDCl_3$) δ -5.0, (q), 16.9 (t), 21.4 (q), 30.1 (t), 115.1 (d), 128.8 (d), 128.9 (d), 133.9 (d), 135.5 (s), 136.8 (s), 138.3 (s), 153.6 (s); **IR** (neat) 3352, 3011, 2919, 1512, 1236, 1087, 798cm^{-1}; **MS** (EI) *m/z* 392 (M^{+} 3%), 377 (10%), 300 (38%), 271 (100%), 255 (21%), 181 (36%), 165 (27%), 91 (30%); **HRMS** calc'd for $C_{23}H_{26}{}^{74}GeO$ 392.1195, found 392.1204, error –2.3ppm;

4-{2-[Dichloro-(4-methylphenyl)germanyl]ethyl}phenol (51)



51

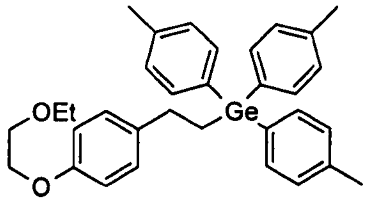
Molecular Weight =355.79
Molecular Formula =$C_{15}H_{16}Cl_2GeO$

A solution of MSA in CH_2Cl_2 (6.03M, 40mL) was added to tritolylgermylphenol **52** (0.406g, 0.869mmol) and the mixture stirred at rt for 2.5 hours. The reaction mixture was then transferred to a large conical flask and neutralised with saturated aqueous $NaHCO_3$ solution (200mL) initially added dropwise, and then stirred for 15 minutes. Phases were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50mL). The organic washings were treated with c.HCl (150mL), the phases separated and the acid layer extracted with further CH_2Cl_2 (2 × 50mL). The organics were combined, dried with $MgSO_4$, filtered, concentrated *in vacuo* and analysed by ^{1}H NMR as before to reveal the presence of dichlorotolylphenol **51** and a trace of chloroditolylphenol **53**.

The crude mixture was partitioned between CH_2Cl_2 (30mL) and aqueous NaOH (0.5M, 60mL). The layers were separated and the basic layer extracted with CH_2Cl_2 (2 × 15mL). The organic washings were combined and extracted with further NaOH (0.5M, 50mL). The organics were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give chloroditolylphenol **53** (0.008g, 0.0194mmol, 2%). Analytical data as above.

The basic layers were combined, filtered to remove precipitates, and then cautiously treated with aqueous HCl (1M, 50mL), before being further acidified with c.HCl (100mL). The now acidic layer was then extracted with CH_2Cl_2 (3 × 50mL), the organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give dichlorotolylphenol **51** as a pale brown oil (0.252g, 0.708mmol, 82%). **R*f*** 0.00 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 2.07 (2H, m, CH_2CH_2Ge), 2.39 (3H, s, $ArCH_3$), 2.94 (2H, m, CH_2CH_2Ge), 4.82 (1H, bs, O*H*), 6.74 (2H, d, *J* 8.5, HOCC*H*CHC), 7.07 (2H, d, *J* 8.5, HOCCHC*H*C), 7.27 (2H, d, *J* 8.0, GeCCHC*H*CCH$_3$), 7.46 (2H, d, *J* 8.0, GeCC*H*CHCCH$_3$); **^{13}C NMR** ($CDCl_3$) δ 21.6 (q), 27.6 (t), 28.5 (t), 115.5 (d), 129.3 (d), 129.6 (d), 132.0 (d), 132.1 (s), 133.8 (s), 142.0 (s), 154.1 (s); **IR** (neat) 3350, 2921, 1597, 1514, 1235, 1090, 799, 695 cm^{-1}; **MS** (EI) *m/z* 356 (5%), 235 (8%), 165 (2%), 120 (100%), 107 (31%), 91 (59%), 65 (32%); **HRMS** calc'd for $C_{15}H_{16}Cl_2{}^{74}GeO$ 355.9790, found 355.9802, error –3.3ppm.

4-{2-[Tri-(4-methyl-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether (66)

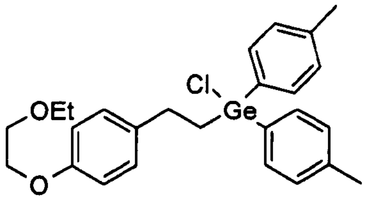


66

Molecular Weight =539.26
Molecular Formula =$C_{33}H_{38}GeO_2$

2-Chloroethyl ethyl ether (1.8mL, 1.78g, 16.4mmol) was added to a solution of tritolylgermylphenol **52** (1.50g, 3.21mmol), cesium carbonate (1.50g, 4.56mmol), and TBAI (0.128g, 0.345mmol) dissolved in MeCN (50mL), and the resulting mixture heated at 80°C for 16 hours. The crude reaction mixture was then partitioned between Et_2O (75mL) and aqueous HCl (1M, 75mL), and the aqueous layer further extracted with Et_2O (2 × 25mL). The organics were combined, dried with $MgSO_4$, and concentrated *in vacuo* before being filtered through silica gel (3 × 6cm, eluting with petrol/EtOAc, 85:15) to give tritolylgermane **66** as a clear colourless oil (1.56g, 2.89mmol, 90%). **R_f** 0.65 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 1.28 (3H, t, *J* 7.0, CH_3CH_2O), 1.81 (2H, m, CH_2CH_2Ge), 2.39 (9H, s, $ArCH_3$), 2.78 (2H, m, CH_2CH_2Ge), 3.63 (2H, q, *J* 7.0, CH_3CH_2O), 3.80 (2H, t, *J* 5.0, OCH_2CH_2OAr), 4.12 (2H, t, *J* 5.0, OCH_2CH_2OAr), 6.85 (2H, d, *J* 8.5, $OCCHCHCCH_2$), 7.11 (2H, d, *J* 8.5, $OCCHCHCCH_2$), 7.22 (6H, d, *J* 8.0, $GeCCHCHCCH_3$), 7.42 (6H, d, *J* 8.0, $GeCCHCHCCH_3$); **^{13}C NMR** ($CDCl_3$) δ 15.3 (q), 16.4 (t), 21.5 (q), 30.3 (t), 66.9 (t), 67.5 (t), 69.1 (t), 114.6 (d), 128.7 (d), 129.1 (d), 133.6 (s), 135.0 (d), 137.2 (s), 138.7 (s), 157.0 (s); **IR** (neat) 2921, 1509, 1245, 1124, 1086, 798 cm^{-1}; **MS** (EI) *m/z* 540 ($M^{\cdot+}$ 4%), 448 (10%), 347 (100%), 271 (15%), 255 (9%), 165 (16%), 91 (20%); **HRMS** calc'd for $C_{33}H_{38}{}^{74}GeO_2$ 540.2084, found 540.2082, error 0.4ppm; **Elemental analysis** expected for $C_{33}H_{38}{}^{74}GeO_2$ C 73.50%, H 7.10%, analysis found C 73.43%, H 7.51%.

4-{2-[Chloro-di-(4-methyl-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether (67)

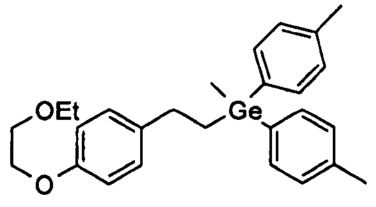


67

Molecular Weight =483.58
Molecular Formula =$C_{26}H_{31}ClGeO_2$

Tritolylgermane **66** (0.275g, 0.510mmol) was dissolved in a solution of MSA in CH_2Cl_2 (0.25M, 12.3mL) and stirred at rt for 55 minutes. The reaction mixture was added dropwise to distilled water (10mL) and shaken, the phases were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20mL). The combined organic layers were shaken with c.HCl (50mL), phases separated and the acid layer extracted with CH_2Cl_2 (2 × 20mL). The organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give chloroditolylgermane **67** as a pale brown oil (0.237g, 0.49mmol, 96%). **R*f*** 0.00 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 1.25 (3H, t, *J* 7.0, CH_3CH_2O), 1.87-1.94 (2H, m, CH_2CH_2Ge), 2.39 (6H, s, $ArCH_3$), 2.81-2.88 (2H, m, CH_2CH_2Ge), 3.61 (2H, q, *J* 7.0, CH_3CH_2O), 3.79 (2H, t, *J* 5.0, OCH_2CH_2OAr), 4.09 (2H, t, *J* 5.0, OCH_2CH_2OAr), 6.82 (2H, d, *J* 8.5, $OCCHCHCCH_2$), 7.09 (2H, d, *J* 8.5, $OCCHCHCCH_2$), 7.24 (4H, d, *J* 8.0, $GeCCHCHCCH_3$), 7.47 (4H, d, *J* 8.0, $GeCCHCHCCH_3$); **^{13}C NMR** ($CDCl_3$) δ 15.2 (q), 21.1 (t), 21.5 (q), 29.1 (t), 66.8 (t), 67.5 (t), 69.0 (t), 114.7 (d), 128.8 (d), 129.4 (d), 132.3 (s), 133.4 (d), 135.6 (s), 140.3 (s), 157.2 (s); **IR** (neat) 2923, 1610, 1511, 1244, 1124, 910, 799, 733cm^{-1}; **MS** (EI) *m/z* 484 (M^{+} 6%), 291 (32%), 248 (35%), 192 (100%), 91 (22%), 45 (39%); **HRMS** calc'd for $C_{26}H_{31}Cl^{74}GeO_2$ 484.1224, found 484.1229, error –0.9 ppm.

4-{2-[Methyl-di-(4-methyl-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether (56)



56

Molecular Weight =463.16
Molecular Formula =$C_{27}H_{34}GeO_2$

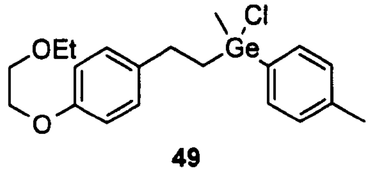
Method 1: Protection of 4-{2-[methyldi-(4-methylphenyl)germanyl]ethyl}phenol

2-Chloroethyl ethyl ether (0.5mL, 0.495g, 4.56mmol) was added to a solution of methylditolylphenol **54** (0.600g, 1.53mmol), cesium carbonate (0.622g, 1.91mmol), and TBAI (0.0557g, 0.151mmol) dissolved in MeCN (16mL), and the resulting mixture heated at 80°C for 17 hours. The crude reaction mixture was then partitioned between EtOAc (20mL) and distilled water (20mL), and the aqueous layer further extracted with EtOAc (2 x 20mL). The organics were combined, dried with $MgSO_4$ and concentrated *in vacuo* before being purified by column chromatography (50g Isolute Silica gel SPE cartridge, eluted with petrol/EtOAc, 19/1) to give methylditolylgermane **56** as a pale brown oil (0.462g, 0.997mmol, 65%). **R*f*** 0.56 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 0.57 (3H, s, GeC*H*$_3$), 1.24 (3H, t, *J* 7.0, C*H*$_3$CH$_2$O), 1.52 (2H, m, CH$_2$C*H*$_2$Ge), 2.34 (6H, s, ArCH$_3$), 2.67 (2H, m, C*H*$_2$CH$_2$Ge), 3.59 (2H, q, *J* 7.0, CH$_3$C*H*$_2$O), 3.77 (2H, t, *J* 5.0, OC*H*$_2$CH$_2$OAr), 4.08 (2H, t, *J* 5.0, OCH$_2$C*H*$_2$OAr), 6.82 (2H, d, *J* 8.5, OCC*H*CHCCH$_2$), 7.06 (2H, d, *J* 8.5, OCCHC*H*CCH$_2$), 7.17 (4H, d, *J* 8.0, GeCCHC$_H$CCH$_3$), 7.37 (4H, d, *J* 8.0, GeCC*H*CHCCH$_3$); **^{13}C NMR** ($CDCl_3$) δ -5.0 (q), 15.2 (q), 16.9 (t), 21.5 (q), 30.2 (t), 66.9 (t), 67.5 (t), 69.1 (t), 114.6 (d), 128.7 (d), 129.0 (d), 134.0 (d), 135.6 (s), 137.0 (s), 138.4 (s), 156.9 (s); **IR** (neat) 2922, 1510, 1245, 1125, 799 cm^{-1}; **MS** (EI) *m/z* 464 (M^{+} 6%), 449 (6%), 347 (41%), 271 (100%), 195 (54%), 181 (49%), 165 (33%), 91 (44%); **HRMS** calc'd for $C_{27}H_{34}{}^{74}GeO_2$ 464.1771, found 464.1785, error -3.2ppm; **Elemental analysis** expected for $C_{27}H_{34}GeO_2$ C 70.02%, H 7.40%, analysis found C 70.31%, H 7.76%.

Method 2: Methylation of 4-{2-[chloro-di-(4-methyl-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether

Methyl magnesium iodide (3.0M in Et_2O, 1mL, 3mmol) was added to a solution of chloroditolylgermane **67** (0.233g, 0.481mmol) dissolved in anhydrous THF (9mL), and the resulting mixture heated at reflux for 22 hours. Distilled water was added dropwise to destroy excess Grignard reagent, and the mixture then partitioned between Et_2O (5mL) and aqueous HCl (5mL), the acid layer was further extracted with Et_2O (2 × 5mL). The organic layers were combined and washed with saturated aqueous $Na_2S_2O_3$ solution (5mL), before being dried with $MgSO_4$, filtered and concentrated *in vacuo* to give methylditolylgermane **56** as a clear colourless oil (0.207g, 0.447mmol, 93%). Analytical data as above.

4-{2-[Chloro-methyl-(4-methyl-phenyl)germanyl]ethyl}-phenyl (2-ethoxy-ethyl) ether (49)



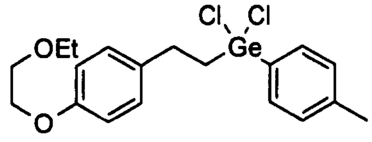
49

Molecular Weight =407.48
Molecular Formula =$C_{20}H_{27}ClGeO_2$

A solution of MSA in CH_2Cl_2 (0.23M, 6mL) was added to methylditolylgermane **56** (0.122g, 0.262mmol) and the mixture stirred for 30 minutes before being added dropwise to saturated aqueous $NaHCO_3$ (10mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 10mL), and the combined organic washings treated with c.HCl (20mL), the phases were separated again, and the acid layer was further extracted with CH_2Cl_2 (2 × 10mL). The combined organic layers were then dried with $MgSO_4$, filtered and concentrated *in vacuo* to give chloromethyltolylgermane **49** as a pale brown oil (0.101g, 2.48mmol, 94%). **R**$_f$ 0.00 (petrol/EtOAc, 9/1); ^{1}**H NMR** ($CDCl_3$) δ 0.79 (3H, s, $GeCH_3$), 1.26 (3H, t, *J* 7.0, CH_3CH_2O), 1.71 (2H, m, CH_2CH_2Ge), 2.39 (3H, s, $ArCH_3$), 2.84 (2H, m, CH_2CH_2Ge), 3.61 (2H, q, *J* 7.0, CH_3CH_2O), 3.79 (2H, t, *J* 5.0, OCH_2CH_2OAr), 4.11 (2H, t, *J* 5.0, OCH_2CH_2OAr), 6.85 (2H, d, *J* 8.5, OCC*H*CHCCH$_2$), 7.10 (2H, d, *J* 8.5, OCCHC*H*CCH$_2$), 7.25 (2H, d, *J* 8.0, GeCCHC*H*CCH$_3$), 7.45 (2H, d, *J* 8.0, GeCC*H*CHCCH$_3$); ^{13}**C NMR** ($CDCl_3$) δ

1.7 (q), 15.2 (q), 21.5 (q), 22.4 (t), 29.1 (t), 66.9 (t), 67.5 (t), 69.0 (t), 114.7 (d), 128.9 (d), 129.4 (d), 132.6 (d), 134.2 (s), 135.2 (s), 140.2 (s), 157.2 (s); **IR** (neat) 2925, 2868, 1610, 1511, 1246, 1197, 1125, 797cm^{-1}; **MS** (EI) *m/z* 408 (M^{+} 10%), 357 (3%), 301 (3%), 215 (24%), 192 (100%), 120 (16%), 91 (17%), 73 (27%), 45 (69%); **HRMS** calc'd for $C_{20}H_{27}Cl^{74}GeO_2$ 408.0911, found 408.0918, error –1.6 ppm.

4-{2-[Dichloro-(4-methyl-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether (50)



50

Molecular Weight =427.90
Molecular Formula =$C_{19}H_{24}Cl_2GeO_2$

Method 1: Ethoxyethyl protection of 4-{2-[dichloro-(4-methylphenyl)germanyl]ethyl}phenol with Et$_4$NI catalyst

Dichlorotolylphenol **51** (0.790g, 2.22mmol), cesium carbonate (0.875g, 2.69mmol), Et$_4$NI (0.0600g, 0.233mmol) and 2-chloroethyl ethyl ether (0.75mL, 0.742g, 6.83mmol) were dissolved in MeCN (20mL) under an N_2 atmosphere and heated at reflux for 17 hours. The resulting crude reaction mixture was hydrolysed with aqueous NaOH (0.5M, 75mL) and then extracted with CH_2Cl_2 (3 × 75mL). The combined organic washings were treated with further aqueous NaOH (2M, 2 × 75mL). The basic washings were retained whilst the CH_2Cl_2 layer was treated with c.HCl (15mL), dried with $MgSO_4$, filtered and concentrated *in vacuo* to give dichlorotolylgermane **50** as a pale brown oil (0.332g, 0.776mmol, 35%). **R*f*** 0.00 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 1.26 (3H, t, *J* 7.0, C*H*$_3$CH$_2$O), 2.09 (2H, m, CH$_2$C*H*$_2$Ge), 2.40 (3H, s, ArC*H*$_3$), 2.96 (2H, m, C*H*$_2$CH$_2$Ge), 3.62 (2H, q, *J* 7.0, CH$_3$C*H*$_2$O), 3.79 (2H, t, *J* 5.0, OC*H*$_2$CH$_2$OAr), 4.10 (2H, t, *J* 5.0, OCH$_2$C*H*$_2$OAr), 6.84 (2H, d, *J* 8.5, OCC*H*CHCCH$_2$), 7.11 (2H, d, *J* 8.5, OCCHC*H*CCH$_2$), 7.27 (2H, d, *J* 8.5, GeCCHC*H*CCH$_3$), 7.47 (2H, d, *J* 8.5, GeCC*H*CHCCH$_3$); **^{13}C NMR** ($CDCl_3$) δ 15.2 (q), 21.6 (q), 27.7 (t), 28.5 (t), 66.9 (t), 67.5 (t), 69.0 (t), 114.8 (d), 129.0 (d), 129.6 (d), 132.0 (d), 132.2 (s), 133.7 (s), 142.0 (s), 157.5 (s); **IR** (neat) 2975, 2926, 2870, 1512, 1248, 1125, 800cm^{-1}; **MS** (EI) *m/z* 428 (M^{+} 16%), 235 (10%), 192

(33%), 120 (39%), 91 (45%), 73 (49%), 45 (100%); **HRMS** calc'd for $C_{19}H_{24}Cl_2{}^{74}GeO_2$ 428.0365, found 428.0352, error 3.0ppm.

The retained basic washings were treated with c.HCl (200mL) and then extracted with CH_2Cl_2 (3 × 75mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give dichlorotolylphenol **51** starting material (0.504g, 1.42mmol, 63%). Analytical data as above.

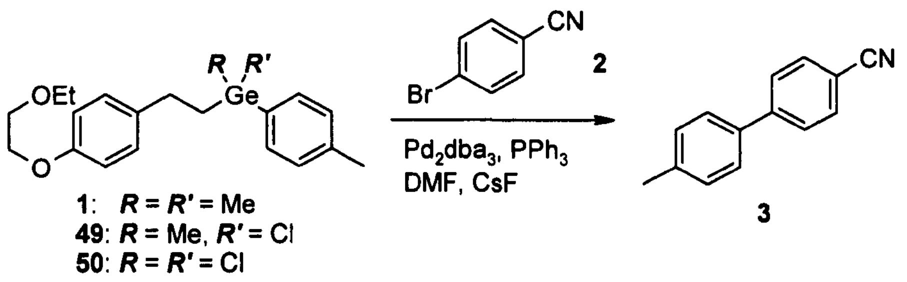
Method 2: Ethoxyethyl protection of 4-{2-[dichloro-(4-methylphenyl)germanyl]ethyl}phenol with CsI catalyst

Dichlorotolylphenol **51** (0.430g, 1.21mmol), cesium carbonate (1.42g, 4.36mmol), CsI (0.0659g, 0.233mmol) and 2-chloroethyl ethyl ether (0.5mL, 0.495g, 4.56mmol) were dissolved in MeCN (8mL) under an N_2 atmosphere and heated at reflux for 17 hours. The resulting crude reaction mixture was partitioned between aqueous NaOH (2M, 3 × 50mL) and CH_2Cl_2 (50mL). The organic washings were treated with c.HCl (75mL), dried with $MgSO_4$, filtered and concentrated *in vacuo* to give dichlorotolylgermane **50** as a pale brown oil (0.330g, 0.771mmol, 64%). Analytical data as above.

Method 3: Electrophilic dearylation of 4-{2-[tri-(4-methyl-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether

A solution of MSA in CH_2Cl_2 (6.04M, 12mL) was added to tritolylgermane **66** (0.141g, 0.261mmol) and stirred at rt for 3 hours, before being added to distilled water (20mL). The phases were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20mL). The combined organic washings were then shaken with c.HCl (50mL), before being separated and the acid layer further extracted with CH_2Cl_2 (2 × 10mL). The organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give dichlorotolylgermane **50** as a pale brown oil (0.109mg, 0.254mmol, 97%). Analytical data as above.

6.2.2.2 Cross-coupling of chloroqermanes



General method

A 3mL reaction vial was charged with germanes **1**, **49**, or **50**, 4-bromobenzonitrile, $Pd_2(dba)_3$, phosphine, and CsF. The reagents were dissolved in DMF (1.5mL), sealed and heated at 150°C for 48 hours. Naphthalene solution (0.01mL, 0.25M) was added to a 25μL sample of crude reaction mixture and diluted with $CHCl_3$ to give 0.5mL of solution. Analysis by quantitative GC/MS gave the following results.

Cross-coupling of tolylgermane 1 and 4-bromobenzonitrile (Figure 4.54)

Reaction 1

Tolylgermane **1** (0.100g, 0.258mmol), 4-bromobenzonitrile (0.0562g, 0.309mmol), Pd_2dba_3 (0.0128g, 0.0140mmol), PPh_3 (0.0135g, 0.0515mmol), CsF (0.0949g, 0.625mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS** $\mathbf{R_t}$ 8.68min; **yield** 4%.

Reaction 2

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0571g, 0.314mmol), Pd_2dba_3 (0.0117g, 0.0128mmol), PPh_3 (0.0133g, 0.0507mmol), CsF (0.108g, 0.711mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS** $\mathbf{R_t}$ 8.68min; **yield** 3%.

Reaction 3

Tolylgermane **1** (0.101g, 0.261mmol), 4-bromobenzonitrile (0.0585g, 0.321mmol), Pd_2dba_3 (0.0119g, 0.0130mmol), PPh_3 (0.0133g, 0.0507mmol), CsF (0.129g, 0.849mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS** $\mathbf{R_t}$ 8.68min; **yield** 4%.

Cross-coupling of chloromethyltolylgermane 49 and 4-bromobenzonitrile (Figure 4.54)

Reaction 1

Chloromethyltolylgermane **49** (0.105g, 0.258mmol), 4-bromobenzonitrile (0.0573g, 0.314mmol), Pd_2dba_3 (0.0153g, 0.0167mmol), PPh_3 (0.0137g, 0.0522mmol), CsF (0.0897g, 0.591mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS** $\mathbf{R_t}$ 8.67min; **yield** 4%.

Reaction 2

Chloromethyltolylgermane **49** (0.105g, 0.258mmol), 4-bromobenzonitrile (0.0570g, 0.313mmol), Pd_2dba_3 (0.0119g, 0.0130mmol), PPh_3 (0.0137g, 0.0522mmol), CsF (0.0982g, 0.646mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS** $\mathbf{R_t}$ 8.67min; **yield** 5%.

Cross-coupling of dichlorotolylgermane 50 and 4-bromobenzonitrile (Figure 4.54)

Reaction 1

Dichlorotolylgermane **50** (0.110g, 0.257mmol), 4-bromobenzonitrile (0.0563g, 0.309mmol), Pd_2dba_3 (0.0136g, 0.0149mmol), PPh_3 (0.0139g, 0.0530mmol), CsF (0.0924g, 0.608mmol). 4-Cyano-4'-methyl-biphenyl; **GC/MS** $\mathbf{R_t}$ 8.67min; **yield** 0.9%.

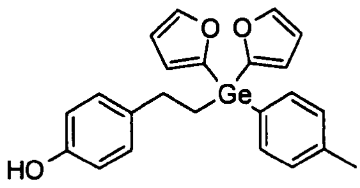
Reaction 2

Dichlorotolylgermane **50** (0.0758g, 0.177mmol), 4-bromobenzonitrile (0.0388g, 0.213mmol), Pd_2dba_3 (0.0077g, 0.00841mmol), PPh_3 (0.0092g, 0.0351mmol), CsF (0.0598g, 0.394mmol) dissolved in anhydrous DMF (1mL). 4-Cyano-4'-methyl-biphenyl; **GC/MS** $\mathbf{R_t}$ 8.67min; **yield** 0.5%.

6.2.3 Approaches towards furylgermane cross-coupling

6.2.3.1 Synthesis of furylgermanes

4-{2-[Di-(2-furyl)-(4-methylphenyl)germanyl]ethyl}phenol (58)

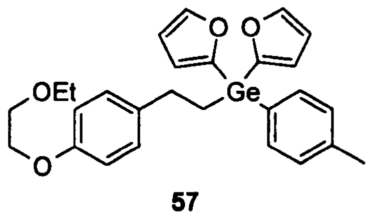


58

Molecular Weight =419.02
Molecular Formula =$C_{23}H_{22}GeO_3$

n-Butyl lithium (2.5M, 2.2mL, 5.5mmol) was added dropwise with stirring to a solution of furan (0.45mL, 0.412g, 6.19mmol) in anhydrous THF (10mL) at 0°C and stirred for 30 minutes. A solution of dichlorotolylphenol **51** (0.502g, 1.41mmol) in anhydrous THF (5mL) was then added dropwise to the solution of furyl lithium at 0°C, the ice bath removed and the resulting mixture allowed to warm to rt over 90 minutes. The mixture was then heated at reflux for 17 hours. Distilled water was cautiously added to destroy any excess organometallic species before the crude reaction mixture was partitioned between distilled water (30mL) and Et_2O (3 × 20mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification with a Silica gel SPE cartridge (10g eluted with cyclohexane → cyclohexane/EtOAc, 19/1 → cyclohexane/EtOAc, 9/1 → cyclohexane/EtOAc, 8/2) to give difuryltolylphenol **58** as a pale brown oil (0.230g, 0.550mmol, 39%). **R*f*** 0.63 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 1.82 (2H, m, $CH_2C\mathit{H}_2Ge$), 2.39 (3H, s, $ArC\mathit{H}_3$), 2.83 (2H, m, $C\mathit{H}_2CH_2Ge$), 5.93 (1H, s, O*H*), 6.48 (2H, m, furyl CH's), 6.73-6.74 (2H, m, furyl CH's), 6.76 (2H, d, *J* 9.0, HOCC*H*CHCC), 7.07 (2H, d, *J* 9.0, HOCCHC*H*C), 7.23 (2H, d, *J* 8.0, $GeCCHC\mathit{H}CCH_3$), 7.48 (2H, d, *J* 8.0, $GeCC\mathit{H}CHCCH_3$), 7.76-7.77 (2H, m, furyl CH's); **^{13}C NMR** ($CDCl_3$) δ 15.9 (t), 20.8 (t), 29.2 (q), 109.0 (d), 114.5 (d), 120.3 (d), 128.3 (d), 128.5 (d), 130.6 (s), 133.5 (d), 135.8 (s), 138.7 (s), 146.6 (d), 152.8 (s), 154.1 (s); **IR** (neat) 3418, 2923, 2853, 1513, 1461, 1377, 1199, 1000, 800cm^{-1}; **MS** (ESI+) *m/z* 443 $[M+Na]^+$ (100%); **HRMS** calc'd for $C_{23}H_{22}O_3{}^{74}GeNa$ 443.0678, found 443.0690, error 2.7ppm.

4-{2-[Di-(2-furyl)-(4-methyl-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether (57)

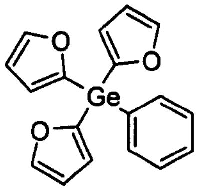


Molecular Weight =491.13
Molecular Formula =$C_{27}H_{30}GeO_4$

57

Difuryltolylphenol **58** (0.190g, 0.454mmol), cesium carbonate (0.163g, 0.501mmol), TBAI (0.0173g, 0.0468mmol) and 2-chloroethyl ethyl ether (0.23mL, 0.227g, 2.10mmol) were dissolved in MeCN (20mL) and heated at reflux for 18.5 hours. The crude reaction mixture was partitioned between distilled water (20mL) and Et_2O (2 × 20mL). The organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* before being filtered through Silica gel (5g SPE cartridge, eluting with cyclohexane/EtOAc, 8/2) to give difuryltolylgermane **57** as a pale brown oil (0.197g, 0.401mmol, 88%). **R*f*** 0.48 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 1.24 (3H, t, *J* 7.0, CH_3CH_2O), 1.79 (2H, m, CH_2CH_2Ge), 2.35 (3H, s, $ArCH_3$), 2.80 (2H, m, CH_2CH_2Ge), 3.59 (2H, q, *J* 7.0, CH_3CH_2O), 3.77 (2H, t, *J* 5.0, OCH_2CH_2OAr), 4.08 (3H, t, *J* 5.0, OCH_2CH_2OAr), 6.44-6.46 (2H, m, furyl CH's), 6.69-6.70 (2H, m, Furyl CH's), 6.81 (2H, d, *J* 9.0, $OCCHCHCCH_2$), 7.08 (2H, d, *J* 9.0, $OCCHCHCCH_2$), 7.19 (2H, d, *J* 8.0, $GeCCHCHCCH_3$), 7.43 (2H, d, *J* 8.0, $GeCCHCHCCH_3$), 7.71 (2H, m, furyl CH's); **^{13}C NMR** ($CDCl_3$) δ 13.9 (t), 15.2 (q), 20.2 (q), 28.5 (t), 65.5 (t), 66.2 (t), 67.7 (t), 108.3 (d), 113.2 (d), 119.6 (d), 127.4 (d), 127.9 (d), 129.9 (s), 132.9 (d), 135.2 (s), 138.0 (s), 145.9 (d), 153.5 (s), 155.7 (s); **IR** (neat) 2924, 2868, 1610, 1510, 1245, 1124, 1002, 800cm^{-1}; **MS** (ESI+) *m/z* 515 $[M+Na]^+$ (100%); **HRMS** calc'd for $C_{27}H_{30}O_4{}^{74}GeNa$ 515.1254, found 515.1240, error –2.6ppm.

Tri-(2-furyl)-phenyl-germane 60[135]



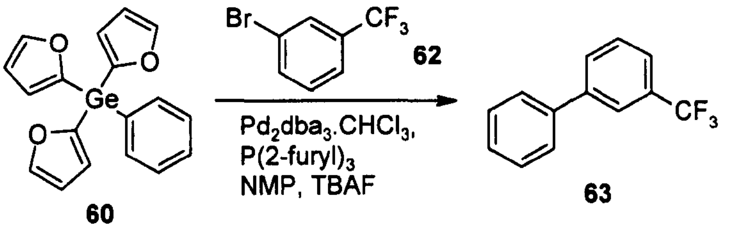
60

Molecular Weight =350.90
Molecular Formula =$C_{18}H_{14}GeO_3$

n-Butyl lithium (2.5M, 8mL, 20.0mmol) was added dropwise with stirring to a solution of furan (1.6mL, 1.50g, 22.0mmol) in anhydrous THF (15mL) at 0°C and stirred for 30 minutes. A solution of phenyltrichlorogermane (1.00g, 3.91mmol) in anhydrous THF (4mL) was then added dropwise to the solution of furyl lithium at 0°C, the ice bath removed and the resulting mixture allowed to warm to rt over 16 hours. Distilled water was cautiously added to destroy any excess organometallic species, before the crude reaction mixture was partitioned between distilled water (30mL) and EtOAc (3 × 30mL). The organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification using a Biotage flash chromatography system with a 50g Silica gel cartridge (eluted with cyclohexane → cyclohexane/EtOAc (19/1) → cyclohexane/EtOAc (9/1) → cyclohexane/EtOAc, 8/2) gave tri-(2-furyl)-phenyl-germane **60** as a white powder (1.11g, 3.15mmol, 81%).[225] **R*f*** 0.61 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 6.50 (3H, dd, *J* 2.0, 3.0, GeCCHC*H*CHO), 6.84 (3H, d, *J* 3.0, furyl C*H*'s), 7.39-7.46 (3H, m, phenyl CH's), 7.64-7.68 (2H, m, phenyl CH's), 7.78 (3H, d, *J* 2.0, furyl CH's); **MS** (EI) *m/z* 352 ($M^{\cdot+}$ 6%), 275 (6%), 218 (6%), 151 (12%), 144 (30%), 134 (100%), 128 (50%), 115 (14%); **melting point** 90.3-93.7°C (*cf.* 92-94°C[225]).

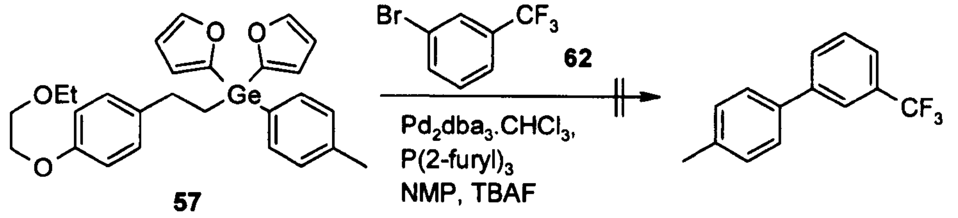
6.2.3.2 Cross-coupling of furylgermanes (Figure 4.58)

Cross-coupling of tri-(2-furyl)phenylgermane (60) with3-bromobenzotrifluoride



Using the method of Oshima,[135] trifurylgermane **60** (0.106g, 0.301mmol), and 3-bromobenzotrifluoride (48μL, 0.0774g, 0.344mmol) were weighed into a round bottom flask and placed in an N_2 atmosphere, before being dissolved in anhydrous NMP (1.4mL). TBAF (1M in THF, 1.6mL, 1.6mmol) was added and the solution stirred at rt for 10 minutes. $Pd_2dba_3 \cdot CHCl_3$ (0.0297g, 0.0287mmol) and $P(2\text{-furyl})_3$ (0.0137g, 0.0590mmol) were dissolved in anhydrous NMP (1.4mL) and added to the reaction mixture, which was then stirred at 100°C for 20 hours. The crude reaction mixture was poured onto water (10mL) and then extracted with EtOAc (3 x 5mL), the organic washings were combined, washed with brine (5mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified with an SPE cartridge (10g Silica gel eluting with cyclohexane) to give 3-(trifluoromethyl)-biphenyl **63**[226] as a clear colourless oil (0.0227g, 0.102mmol, 34%). **R_f** 0.89 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 7.40-7.84 (9H, m, aryl CH's); **MS** (EI) *m/z* 222 (M^+ 100%), 201 (22%), 152 (41%), 76 (6%), 75 (6%).

Cross-coupling of difuryltolylgermane 57 and 3-bromobenzotrifluoride



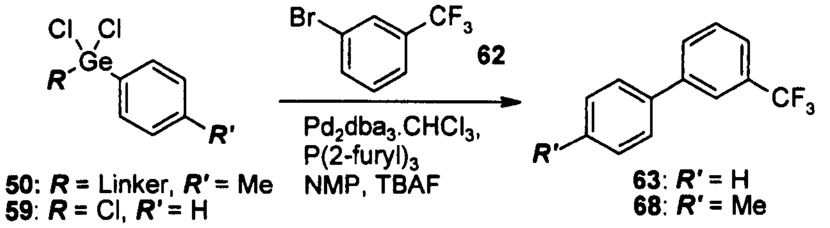
Using the method of Oshima above, with difuryltolylgermane **57** (0.103g, 0.210mmol), 3-bromobenzotrifluoride (35μL, 0.0564g, 0.251mmol), and TBAF (1M in THF, 0.6mL, 0.6mmol) in NMP (0.9mL). $Pd_2dba_3 \cdot CHCl_3$ (0.0231g, 0.0223mmol) and P(2-furyl)$_3$ (0.0113g, 0.0487mmol) in NMP (0.9mL). The residue was purified with an SPE cartridge (10g Silica gel eluting with petrol/EtOAc, 19/1 → petrol/EtOAc, 8/2) to give difuryltolylgermane **57** (0.0205g, 0.0418mmol, 20%). Analytical data as above.

Reaction of tri-(2-furyl)-phenyl-germane with TBAF

TBAF (1.0M in THF, 0.450mL, 0.450mmol) was added to tri-(2-furyl)-phenyl-germane **60** (0.0388g, 0.111mmol) was dissolved in anhydrous THF (1mL) and stirred at rt for 3 hours, after which TLC analysis revealed that some starting material still remained. The mixture was then heated at reflux for 4 hours, at which point TLC revealed that all starting material had been consumed. The crude reaction mixture was then analysed by ESI- FIA/MS to tentatively reveal the presence of ions at *m/z* 203, tentatively assigned as $[PhGeF(OH)_2\text{-}H]^-$, and *m/z* 183, tentatively assigned as $[PhGeO_2]^-$.

6.2.4 Further approaches towards chlorogermane cross-coupling

6.2.4.1 Chlorogermane cross-coupling with fluoride activator following the method of Oshima



Cross-coupling of dichlorotolylgermane 50 with 3-bromobenzotrifluoride (Figure 4.64)

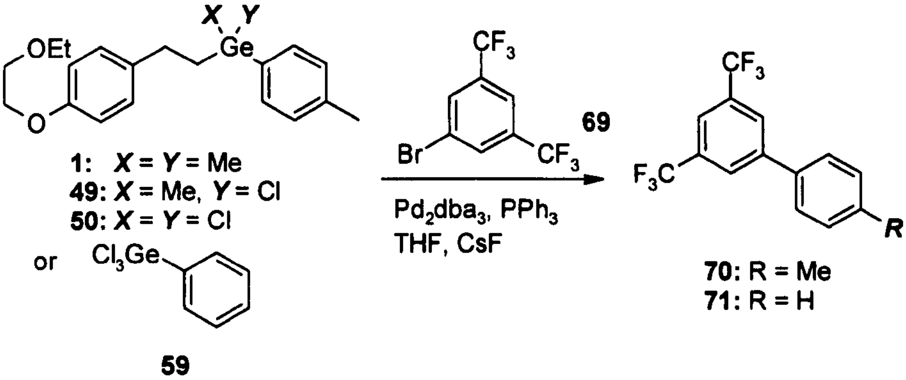
Using the method of Oshima above, with dichlorotolylgermane **50** (0.0851g, 0.199mmol), 3-Bromobenzotrifluoride (35μL, 0.0565g, 0.251mmol) and TBAF (1,0M in THF, 0.6mL, 0.6mmol) in NMP (1mL), and also $Pd_2(dba)_3 \cdot CHCl_3$ (0.0110g, 0.0106mmol) and $P(2\text{-furyl})_3$ (0.0051g, 0.0220mmol) in NMP (1mL). The residue was purified with an SPE cartridge (10g Silica gel eluting with cyclohexane) to give 4-methyl-3'-trifluoromethyl-biphenyl **68**[227] as a clear colourless oil (0.0034g, 0.0144mmol, 7%). **R_f** 0.87 (petrol/EtOAc, 19/1); **^{1}H NMR** ($CDCl_3$) δ 2.42 (3H, s, ArCH_3), 7.49-7.78 (m, 8H, Ar CH's); **MS** *m/z* (EI) 236 (M^+ 100%), 167 (73%), 152 (4%), 91 (12%).

Cross-coupling trichlorophenylgermane with 3-bromobenzotrifluoride (Figure 4.65)

Using the method of Oshima above, with trichlorophenylgermane **59** (35μL, 0.0554g, 0.217mmol), 3-Bromobenzotrifluoride (35μL, 0.0565g, 0.251mmol) and TBAF (1,0M in THF, 1.0mL, 1.0mmol) in NMP (1mL), and $Pd_2dba_3 \cdot CHCl_3$ (0.0114g, 0.0110mmol) and $P(2\text{-furyl})_3$ (0.0048g, 0.0207mmol) in NMP (1mL). GC/MS indicated the presence of no desired product.

6.2.4.2 Chloroqermane cross-coupling with hydroxide activators following the method of Hiyama[54]

Hydroxide mediated Cross-coupling with 3,5-bis(trifluoromethyl)bromobenzene (Figures 4.67 and 4.68)



Cross-coupling of dichlorotolylgermane (50)

Powdered sodium hydroxide (0.0464g, 1.16mmol) was added to dichlorotolylgermane **50** (0.101g, 0.235mmol) dissolved in THF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0118g, 0.0526mmol) and triphenylphosphine (0.0256g, 0.0976mmol) were dissolved in THF (2mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (34μL, 0.057g, 0.195mmol). The reaction mixture was then heated at reflux for 24 hours, before being partitioned between Et_2O (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*, before being purified on a Silica SPE cartridge (5g, eluting with cyclohexane) to give 4-methyl-3',5'-bis-trifluoromethyl-biphenyl **70**[227] as a clear liquid (0.0189g, 0.0622mmol, 32%). **R*f*** 0.65 (cyclohexane); **^{1}H NMR** ($CDCl_3$) δ 2.44 (3H, s, ArC*H*$_3$), 7.33 (2H, d, *J* 8.0, CH_3CC*H*CHCAr), 7.52 (2H, d, *J* 8.0, CH_3CCHC*H*CAr), 7.84 (1H, s), CF_3CC*H*CCF_3, 8.01 (2H, s, ArCC*H*CCF_3); **MS** *m/z* (EI) 304 (M^{+} 91%), 285 (19%), 235 (66%), 215 (39%), 165 (100%), 91 (66%), 69 (25%).

Cross-coupling of chloromethyltolylgermane (49)

Powdered sodium hydroxide (0.0660g, 1.65mmol) was added to chloromethyltolylgermane **49** (0.107g, 0.263mmol) dissolved in THF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0315g, 0.140mmol) and triphenylphosphine (0.0710g, 0.271mmol) were dissolved in THF (5mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (38μL, 0.0645g, 0.220mmol). The reaction mixture was then heated at reflux for 24 hours, before being partitioned between Et_2O (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. GC/MS of the crude reaction mixture indicated only the presence of starting material 3,5-bis-trifluoromethyl-bromo-benzene: **R*f*** 0.75 (cyclohexane); **^{1}H NMR** ($CDCl_3$) δ 7.84 (1H, s, $CF_3CC\mathit{H}CCF_3$), 7.98 (2H, s, $BrCC\mathit{H}CCF_3$); **MS** EI *m/z* 292 (M^{+} 57%), 273 (19%), 223 (7%), 213 (100%), 163 (67%), 144 (56%), 75 (79%), 69 (47%).

Cross-coupling of tolylgermane (1)

Powdered sodium hydroxide (0.0507g, 1.26mmol) was added to dichlorotolylgermane **50** (0.101g, 0.261mmol) dissolved in THF (1mL), and then stirred at rt for 3 hours.

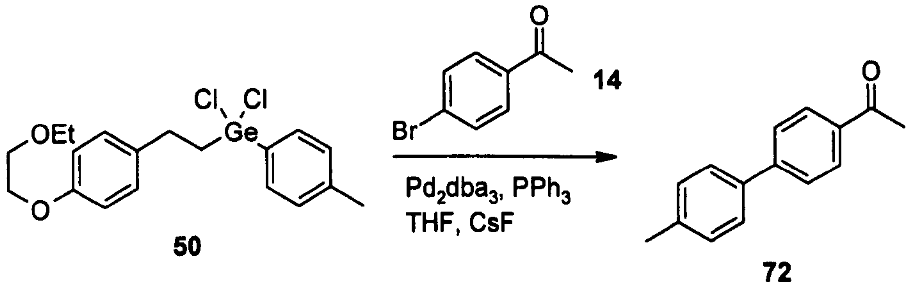
Palladium(II) acetate (0.0315g, 0.140mmol) and triphenylphosphine (0.0710g, 0.271mmol) were dissolved in THF (5mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (38μL, 0.0645g, 0.220mmol). The reaction mixture was then heated at reflux for 24 hours, before being partitioned between Et_2O (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. GC/MS of the crude reaction mixture indicated only the presence of starting material 3,5-bis-trifluoromethyl-bromo-benzene. Analytical data as above.

Cross-coupling of phenyltrichlorogermane (59)

Powdered sodium hydroxide (0.0547g, 1.37mmol) was added to phenyltrichlorogermane **59** (42.5μL, 0.0673g, 0.262mmol) dissolved in THF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0118g, 0.0526mmol) and triphenylphosphine (0.0256g, 0.0976mmol) were dissolved in THF (2mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (34μL, 0.057g, 0.195mmol). The reaction mixture was then heated at reflux for 24 hours, before being partitioned between Et_2O (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*, before being purified on a Silica SPE cartridge (5g, eluting with cyclohexane) to give 3,5-bis-trifluoromethyl-biphenyl **71** as a clear liquid (0.0273g, 0.0941mmol, 48%). **R*f*** 0.78 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 7.46-7.64 (5H, m, phenyl CH's), 7.87 (1H, s, CF_3CC*H*CCF_3), 8.03 (2H, s, PhCC*H*CCF_3); **^{13}C NMR** ($CDCl_3$) δ 120.9 (d), 127.3 (d), 127.5 (d), 128.9 (d), 129.3 (d), 4 quaternary carbons not seen; **IR** (neat) 3070, 2928, 1383, 1350, 1279, 1177, 1134, 1063, 896, 764, 706, 683cm^{-1}; **MS** *m/z* (EI) 290 (M^+ 100%), 271 (14%), 221 (15%), 201 (42%), 152 (35%), 75 (8%), 69 (6%); **HRMS** calc'd for $C_{14}H_8F_6$ 290.0530, found 290.0542, error –4.1ppm.

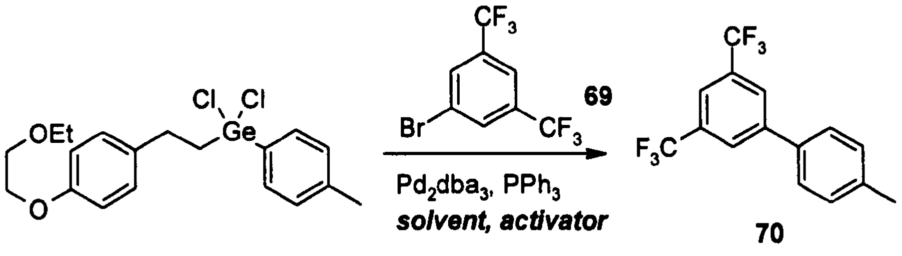
Hydroxide mediated cross-coupling of dichlorotolylgermane (50) with 4-bromoacetophenone (figure 4.70)



Powdered sodium hydroxide (0.0556g, 1.39mmol) was added to dichlorotolylgermane **50** (0.100g, 0.234mmol) dissolved in THF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0104g, 0.0463mmol) and triphenylphosphine (0.0230g, 0.0876mmol) were dissolved in THF (2mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 4-bromo-acetophenone (0.0421g, 0.211mmol). The reaction mixture was then heated at reflux for 24 hours, before being partitioned between EtOAc (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with MgSO$_4$, filtered and concentrated *in vacuo*. Purification was carried out by mass-directed automated preparative LC/MS to give 4-acetyl-4'-methyl-biphenyl 72[213] as a white powder (0.0124g, 0.0590mmol, 28%): **R$_f$** 0.41 (petrol/EtOAc, 9/1); **^{1}H NMR** (CDCl$_3$) δ 2.41 (3H, s, CH$_3$CAr), 2.64 (3H, sCH$_3$COAr), 7.28 (2H, d, *J* 8.0, CH$_3$CC*H*CHCAr), 7.54 (2H, d, *J* 8.0, CH$_3$CCHC*H*CAr), 7.67 (2H, d, *J* 8.0, ArCC*H*CHCCOCH$_3$), 8.02 (2H, d, *J* 8.0, ArCCHC*H*CCOCH$_3$); **MS** (ESI+) *m/z* 211 [M+H$^+$]; (EI) *m/z* 210 (M$^{\cdot+}$ 42%), 195 (100%), 165 (25%), 152 (39%); **LC R$_t$** 3.49min; **Melting point** 116.9-118.3°C (*cf.* 114-115°C[228], 121-122°C[229]).

6.2.4.3 Cross-coupling of dichlorotolylgermane (50) with 3,5-bis-trifluoromethyl-bromo-benzene using alternate activators (Figure 4.69)



Aqueous NaOH mediated cross-coupling at 60°C

Aqueous sodium hydroxide (2.0M, 0.7mL, 1.40mmol) was added to a solution of dichlorotolylgermane **50** (0.0907g, 0.212mmol) dissolved in THF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0154g, 0.0686mmol) and triphenylphosphine (0.0362g, 0.138mmol) were dissolved in THF (3mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (31μL, 0.0527g, 0.180mmol). The reaction mixture was then heated at reflux for 24 hours, before being partitioned between EtOAc (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. GC/MS of the crude reaction mixture indicated only the presence of starting aryl bromide. Analytical data as above.

CsOH mediated cross-coupling at 60°C

Cesium hydroxide monohydrate (0.241g 1.44mmol) was added to a solution of dichlorotolylgermane **50** (0.0748g, 0.175mmol) dissolved in THF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0154g, 0.0686mmol) and triphenylphosphine (0.0362g, 0.138mmol) were dissolved in THF (3mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (31μL, 0.0527g, 0.180mmol). The reaction mixture was then heated at reflux for 24 hours, before being partitioned between EtOAc (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. GC/MS of the crude reaction mixture indicated only the presence of starting aryl bromide. Analytical data as above.

NaOH mediated cross-coupling at 120°C

Powdered sodium hydroxide (0.0548, 1.37mmol) was added to a solution of dichlorotolylgermane **50** (0.0970g, 0.227mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0212g, 0.0944mmol) and triphenylphosphine (0.0499g, 0.190mmol) were dissolved in DMF (4mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (31μL, 0.0527g, 0.180mmol). The reaction mixture was then heated at 127°C for 24 hours, before being partitioned between EtOAc (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. GC/MS of the crude reaction mixture indicated only the presence of des-bromo starting material 1,3-bis-trifluoromethyl-benzene: **MS** (EI) *m/z* 214 (M^{+} 88%), 195 (92%), 164 (40%), 145 (100%), 75 (23%), 69 (13%).

Aqueous NaOH mediated cross-coupling at 120°C

Aqueous sodium hydroxide (2.0M, 0.7mL, 1.40mmol) was added to a solution of dichlorotolylgermane **50** (0.0933g, 0.217mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0212g, 0.0944mmol) and triphenylphosphine (0.0499g, 0.190mmol) were dissolved in DMF (4mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (31μL, 0.0527g, 0.180mmol). The reaction mixture was then heated at 127°C for 24 hours, before being partitioned between EtOAc (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. GC/MS of the crude reaction mixture indicated only the presence of des-bromo starting material 1,3-bis-trifluoromethyl-benzene: Analytical data as above.

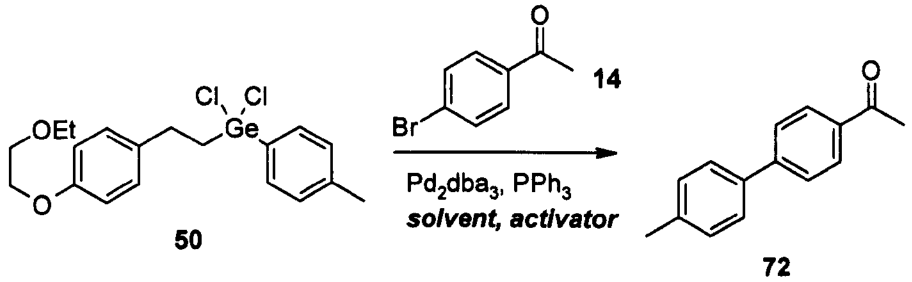
KF mediated cross-coupling at 120°C

Powdered potassium fluoride (0.0820, 1.41mmol) was added to a solution of dichlorotolylgermane **50** (0.0897g, 0.210mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0212g, 0.0944mmol) and triphenylphosphine (0.0499g, 0.190mmol) were dissolved in DMF (4mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bis-trifluoromethyl-bromo-benzene (31μL, 0.0527g, 0.180mmol). The reaction mixture was then heated at 127°C for 24 hours, before being partitioned between EtOAc (3 × 10mL) and distilled water (10mL). Organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*.

Purification using Silica gel SPE cartridge eluting with cyclohexane gave 4-methyl-3',5'-bis-trifluoromethyl-biphenyl **70** as a clear colourless oil (0.0341g, 0.112mmol, 62%). Analytical data as above.

6.2.4.4 Optimisation of cross-coupling of dichlorotolylgermane (50) with 4-bromo-acetophenone



Hydroxide mediated phosphine screen in THF (Figure 4.70)

Dichlorotolylgermane **50** (0.850g, 1.99mmol) was dissolved in THF (10.25mL). Portions of the resulting solution (0.194M, 0.5mL, 0.0969mmol) were added to sixteen reaction vials in a greenhouse parallel reactor vessel (A1-A5, B1-B3, C1-C5, D1-D3). Powdered sodium hydroxide was then added to eight vials (A1 0.035g, 0.875mmol; A2 0.0331g, 0.828mmol; A3 0.0440g, 1.10mmol; A4 0.0315g, 0.788mmol; A5 0.0303g, 0.758mmol; B1 0.0424g, 1.06mmol; B2 0.0354g, 0.885mmol; B3 0.0369g, 0.923mmol), and aqueous sodium hydroxide to eight vials (2M, 0.35mL in C1, C2, C3, C4, C5, D1, D2, and D3) and the resulting mixtures stirred for 5 hours.

Palladium(II) acetate (0.0673g, 0.300mmol) was dissolved in THF (30mL) and 3mL portions (0.01M, 0.0300mmol) added to triphenylphosphine (0.0159g, 0.0606mmol), tri(*o*-tolyl)phosphine (0.0184g, 0.0605mmol), tri-2-furylphosphine (0.0139g, 0.0599mmol), tris-(4-fluorophenyl)phosphine (0.0190g, 0.0601mmol), dppp (0.0123g, 0.0298mmol), dppf (0.0164g, 0.0296mmol), and IMes·HCl (0.0205g, 0.0601mmol). An eighth 3mL portion was measured out to provide a sample of ligandless catalyst. The resulting mixtures were then stirred at rt for 1 hour.

4-Bromo-acetophenone (0.421g, 2.12mmol) was dissolved in THF (10.5mL) and 0.5mL portions (0.201M, 0.101mmol) added to each reaction vial. Catalyst solutions (2mL) were then added to the reactions: triphenylphosphine (A1 and C1), tri(*o*-tolyl)phosphine (A2 and C2), tri-2-furylphosphine (A3 and C3), tris-(*p*-fluorophenyl)phosphine (A4 and C4), dppp (A5 and C5), dppf (B1 and D1), IMes·HCl (B2 and D2) and palladium(II) acetate solution (B3 and D3). The reactions were then heated to 60°C for 22 hours.

An aliquot (0.5mL) of each reaction was added to MeCN (0.25mL) in a 96 well filter block, the mixtures were then filtered and each well rinsed with further MeCN (0.25mL). Each filtrate was then sampled (50μL) and further diluted with MeOH (100μL) before being submitted for ESI LC/MS. The samples using solid sodium hydroxide suffered from precipitation problems and could not be analysed.

The ratio of the LC/UV peak areas of desired product **72** (**R**$_t$ 3.49min, *m/z* 211 [M+H$^+$]) divided by the LC/UV peak area of starting materials (4-bromoacetophenone **14** **R**$_t$ 2.89min, not ionised; dichlorogermane **50** **R**$_t$ 2.94min, *m/z* 392 hydrolysis product) is as follows:

	NaOH (s) 60°C	**NaOH (aq) 60°C**
PPh_3	-	0.12
P(*o*-Tol)$_3$	-	0.25
P(2-furyl)$_3$	-	0.12
P(*p*-C_6H_4F)$_3$	-	0
Dppp	-	0.15
Dppf	-	0.2
IMes·HCl	-	0
Ligandless	-	0

Hydroxide mediated phosphine screen in DMF (Figure 4.70)

Dichlorotolylgermane **50** (1.52g, 3.55mmol) was dissolved in DMF (15.25mL). Portions of the resulting solution (0.233M, 0.5mL, 0.117mmol) were added to sixteen reaction vials in a greenhouse parallel reactor vessel (A1-A5, B1-B3, C1-C5, D1-D3). Powdered sodium hydroxide was then added to eight vials (A1 0.0313g, 0.783mmol; A2 0.0443g, 1.11mmol; A3 0.0365g, 0.913mmol; A4 0.0346g, 0.865mmol; A5 0.0302g, 0.755mmol; B1 0.0337g, 0.843mmol; B2 0.0315g, 0.788mmol; B30.0399g, 0.998mmol), and aqueous sodium hydroxide to eight vials (2M, 0.35mL in C1, C2, C3, C4, C5, D1, D2, and D3) and the resulting mixtures stirred for 5 hours.

Palladium(II) acetate (0.0917g, 0.408mmol) was dissolved in DMF (40mL) and 4mL portions (0.0102M, 0.0408mmol) added to triphenylphosphine (0.0208g, 0.0793mmol), tri(*o*-tolyl)phosphine (0.0244g, 0.0802mmol), tri-2-furylphosphine (0.0185g, 0.0797mmol), tris-(4-fluorophenyl)phosphine (0.0253g, 0.0799mmol), dppp (0.0164g, 0.0398mmol), dppf (0.0220g, 0.0397mmol), and IMes·HCl (0.0137g, 0.0402mmol). The resulting mixtures were then stirred at rt for 1 hour.

4-Bromo-acetophenone (0.618g, 3.10mmol) was dissolved in DMF (15.5mL) and 0.5mL portions (0.200M, 0.100mmol) added to each reaction vial. Catalyst solutions (2mL) were then added to the reactions: triphenylphosphine (A1 and C1), tri(*o*-tolyl)phosphine (A2 and C2), tri-2-furylphosphine (A3 and C3), tris-(4-fluorophenyl)phosphine (A4 and C4), dppp (A5 and C5), dppf (B1 and D1), IMes·HCl (B2 and D2) and palladium(II) acetate solution (B3 and D3). The reactions were then heated to 120°C for 22 hours.

The ratio of the LC/UV peak areas of desired product **72** divided by the LC/UV peak area of starting materials **14** and **50** is as follows:

	NaOH (s) 120°C	**NaOH (aq) 120°C**
PPh_3	0	0
$P(o\text{-}Tol)_3$	1.76	0
$P(2\text{-furyl})_3$	1.2	0
$P(p\text{-}C_6H_4F)_3$	0.59	0
Dppp	0.95	0
Dppf	0	0
IMes·HCl	0	0
Ligandless	0.4	0

Fluoride mediated phosphine screen in DMF (Figure 4.70)

Dichlorotolylgermane **50** (1.52g, 3.55mmol) was dissolved in DMF (15.25mL). Portions of the resulting solution (0.233M, 0.5mL, 0.117mmol) were added to eight reaction vials in a greenhouse parallel reactor vessel (A1-A5, B1-B3). Potassium fluoride was then added (A1 0.0442g, 0.761mmol; A2 0.0463g, 0.797mmol; A3

0.0479g, 0.824mmol; A4 0.0513g, 0.883mmol; A5 0.0457g, 0.787mmol; B1 0.0429g, 0.738mmol; B2 0.0519g, 0.893mmol; B30.0445g, 0.766mmol) and the resulting mixtures stirred for 5 hours.

Palladium(II) acetate (0.0917g, 0.408mmol) was dissolved in DMF (40mL) and 4mL portions (0.0102M, 0.0408mmol) added to triphenylphosphine (0.0208g, 0.0793mmol), tri(*o*-tolyl)phosphine (0.0244g, 0.0802mmol), tri-2-furylphosphine (0.0185g, 0.0797mmol), tris-(4-fluorophenyl)phosphine (0.0253g, 0.0799mmol), dppp (0.0164g, 0.0398mmol), dppf (0.0220g, 0.0397mmol), and IMes·HCl (0.0137g, 0.0402mmol). The resulting mixtures were then stirred at rt for 1 hour.

4-Bromo-acetophenone (0.618g, 3.10mmol) was dissolved in DMF (15.5mL) and 0.5mL portions (0.200M, 0.100mmol) added to each reaction vial. Catalyst solutions (2mL) were then added to the reactions: triphenylphosphine (A1), tri(*o*-tolyl)phosphine (A2), tri-2-furylphosphine (A3), tris-(4-fluorophenyl)phosphine (A4), dppp (A5), dppf (B1), IMes·HCl (B2) and palladium(II) acetate solution (B3). The reactions were then heated to 120°C for 22 hours.

The ratio of the LC/UV peak areas of desired product **72** divided by the LC/UV peak area of starting materials **14** and **50** is as follows:

	KF 120°C
PPh_3	1.19
P(*o*-Tol)$_3$	0.29
P(2-furyl)$_3$	0.98
P(*p*-C_6H_4F)$_3$	1.92
Dppp	2.21
Dppf	1.09
IMes·HCl	2.11
Ligandless	1.65

Isolated yields (5g Silica gel SPE cartridge, eluted with cyclohexane → petrol/EtOAc, 19/1) are as follows:

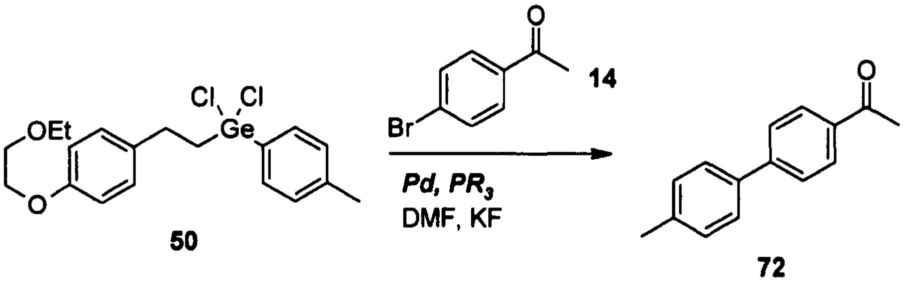
PPh_3: 4-acetyl-4'-methyl-biphenyl **72** as a white amorphous powder (0.0022g, 0.0105mmol, 10.5%). Analytical data as previous.

$P(p\text{-}C_6H_4F)_3$: 4-acetyl-4'-methyl-biphenyl **72** as a white amorphous powder (0.0071g, 0.0338mmol, 34%). Analytical data as previous.

Dppp: 4-acetyl-4'-methyl-biphenyl **72** as a white amorphous powder (0.0042g, 0.0200mmol, 20%). Analytical data as previous.

IMes·HCl: 4-acetyl-4'-methyl-biphenyl **72** as a white amorphous powder (0.0080g, 0.0380mmol, 38%). Analytical data as previous.

Palladium catalyst screen (Figure 4.71)



Dichlorotolylgermane **50** (1.00g, 2.34mmol) was dissolved in DMF (10.5mL). Portions of the resulting solution (0.223M, 0.5mL, 0.111mmol) were added to twenty reaction vials in a greenhouse parallel reactor vessel (A1-A5, B1-B5, C1-C5, D1-D5). Potassium fluoride was then added to the vials (A1 0.0423g, 0.728mmol; A2 0.0496g, 0.854mmol; A3 0.0485g, 0.835mmol; A4 0.0424g, 0.730mmol; A5 0.0429g, 0.738mmol; B1 0.0418g, 0.719mmol; B2 0.0473g, 0.814mmol; B3 0.0473g, 0.814mmol; B4 0.0513g, 0.883mmol; B5 0.0511g, 0.880mmol; C1 0.0456g, 0.785mmol; C2 0.0481g, 0.828mmol; C3 0.0479g, 0.824mmol; C4 0.0515g, 0.886mmol; C5 0.0593g, 1.02mmol; D1 0.0448g, 0.771mmol; D2 0.0511g, 0.880mmol; D3 0.0509g, 0.876mmol; D4 0.0507g, 0.873mmol; D5 0.0499g, 0.859mmol) and the resulting mixtures stirred for 3 hours.

Palladium(II) acetate (0.0139g, 0.0619mmol), $PdCl_2(MeCN)_2$ (0.0157g, 0.0605mmol), Pd_2dba_3 (0.0554g, 0.0605mmol), $[PdCl(C_3H_5)]_2$ (0.0225g, 0.0615mmol), and $Pd(PPh_3)_4$ (0.0681g, 0.0589mmol) were each dissolved in DMF (3mL). Triphenylphosphine (0.0256g, 0.0976mmol), tris-(4-fluorophenyl)phosphine (0.0315g, 0.0996mmol), dppp (0.0264g, 0.0640mmol), and IMes·HCl (0.0171g, 0.0502mmol) were each dissolved in DMF (2.5mL). 0.5mL of each palladium solution was then combined with 0.55mL of each phosphine solution to give a 1.05mL solution of each catalyst combination. 1mL of each catalyst solution was then added reaction vials as follows: A1 $Pd(OAc)_2/PPh_3$; A2 $PdCl_2(MeCN)_2$/ PPh_3; A3 $[PdCl(C_3H_5)]_2/PPh_3$; A4 Pd_2dba_3/PPh_3; A5 $Pd(PPh_3)_4$; B1 $Pd(OAc)_2/P(p\text{-}C_6H_4F)_3$; B2 $PdCl_2(MeCN)_2$/ $P(p\text{-}C_6H_4F)_3$; B3 $[PdCl(C_3H_5)]_2$/ $P(p\text{-}C_6H_4F)_3$; B4 Pd_2dba_3/ $P(p\text{-}C_6H_4F)_3$; B5 $Pd(PPh_3)_4$/ $P(p\text{-}C_6H_4F)_3$; C1 $Pd(OAc)_2$/dppp; C2 $PdCl_2(MeCN)_2$/ dppp; C3 $[PdCl(C_3H_5)]_2$/ dppp; C4 Pd_2dba_3/ dppp; C5 $Pd(PPh_3)_4$/ dppp; D1 $Pd(OAc)_2$/IMes·HCl; D2 $PdCl_2(MeCN)_2$/ IMes·HCl; D3 $[PdCl(C_3H_5)]_2$/ IMes·HCl; D4 Pd_2dba_3/ IMes·HCl; D5 $Pd(PPh_3)_4$/ IMes·HCl. Finally, 4-bromo-acetophenone (0.417g, 2.09mmol) was dissolved in DMF (10.5mL) and 0.5mL of the resulting solution (0.200M, 0.0998mmol) was added to each reaction vial. The reactions were then heated at 120°C for 24 hours. After the reaction solutions had cooled and settled 0.1mL of each was removed and diluted with MeOH (0.4mL) before being analysed by LC/MS as before.

	$Pd(OAc)_2$	**$PdCl_2(MeCN)_2$**	**APC dimer**	**Pd_2dba_3**	**$Pd(PPh_3)_4$**	**Σ**
PPh_3	1.26	2.48	0.71	1.26	1.35 [a]	7.06
$P(p\text{-}C_6H_4F)_3$	1.53	0.48	0.82	1.52	1.65	6.00
Dppp[b]	2.52	2.73	0.89	1.34	1.81	9.30
IMes·HCl[b]	2.15	2.19	1.88	0.22	0.98	7.42
Σ	7.47	7.87	4.30	4.35	5.79	

(a) No extra PPh_3 co-catalyst was added

Cross-coupling using $Pd(OAc)_2/PPh_3$ catalyst (Figure 4.72)

Powdered potassium fluoride (0.0906, 1.56mmol) was added to a solution of dichlorotolylgermane **50** (0.110g, 0.257mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0079g, 0.0351mmol) and triphenylphosphine (0.0165g, 0.0629mmol) were dissolved in DMF (1.5mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 4-bromobenzophenone (0.0414g, 0.208mmol). The reaction mixture was then heated at 127°C for 24 hours, before being partitioned between CH_2Cl_2 (5mL) and distilled water (5mL) and then filtered through a hydrophobic frit, which was rinsed with a further 2mL CH_2Cl_2. The combined organics were washed with water (5mL), and filtered through a hydrophobic frit, which was again rinsed with CH_2Cl_2 (2mL). Organics were once more combined and concentrated *in vacuo*. Purification using Silica gel SPE cartridge eluting with petrol → petrol/EtOAc, 97/3 gave 4-acetyl-4'-methyl-biphenyl **72** as a white powder (0.0254g, 0.121mmol, 58%). Analytical data as above.

Cross-coupling using Pd(OAc)$_2$/dppp catalyst (Figure 4.72)

Powdered potassium fluoride (0.0944, 1.62mmol) was added to a solution of dichlorotolylgermane **50** (0.110g, 0.257mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

Palladium(II) acetate (0.0074g, 0.0330mmol) and dppp (0.0133g, 0.0322mmol) were dissolved in DMF (1.5mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 4-bromobenzophenone (0.0449g, 0.226mmol). The reaction mixture was then heated at 127°C for 24 hours, before being partitioned between CH_2Cl_2 (5mL) and distilled water (5mL) and then filtered through a hydrophobic frit, which was rinsed with a further 2mL CH_2Cl_2. The combined organics were washed with water (5mL), and filtered through a hydrophobic frit, which was again rinsed with CH_2Cl_2 (2mL). Organics were once more combined and concentrated *in vacuo*. Purification using Silica gel SPE cartridge eluting with petrol → petrol/EtOAc, 97/3 gave 4-acetyl-4'-methyl-biphenyl **72** as a white powder (0.0259g, 0.123mmol, 54%). Analytical data as above.

Cross-coupling using PdCl$_2$(MeCN)$_2$/PPh$_3$ catalyst (Figure 4.72)

Powdered potassium fluoride (0.0918, 1.58mmol) was added to a solution of dichlorotolylgermane **50** (0.111g, 0.259mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

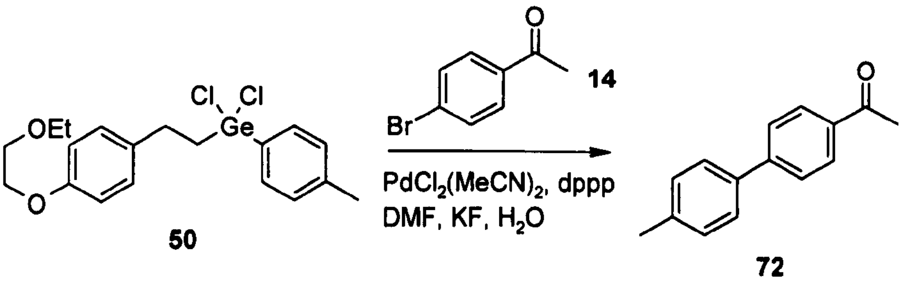
$PdCl_2(MeCN)_2$ (0.0083g, 0.0319mmol) and triphenylphosphine (0.0166g, 0.0633mmol) were dissolved in DMF (1.5mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 4-bromobenzophenone (0.0452g, 0.227mmol). The reaction mixture was then heated at 127°C for 24 hours, before being partitioned between CH_2Cl_2 (5mL) and distilled water (5mL) and then filtered through a hydrophobic frit, which was rinsed with a further 2mL CH_2Cl_2. The combined organics were washed with water (5mL), and filtered through a hydrophobic frit, which was again rinsed with CH_2Cl_2 (2mL). Organics were once more combined and concentrated *in vacuo*. Purification using Silica gel SPE cartridge eluting with petrol → petrol/EtOAc, 97/3 gave 4-acetyl-4'-methyl-biphenyl **72** as a white powder (0.0240g, 0.114mmol, 50%). Analytical data as above.

Cross-coupling using $PdCl_2(MeCN)_2$/dppp catalyst (Figure 4.72)

Powdered potassium fluoride (0.0926, 1.59mmol) was added to a solution of dichlorotolylgermane **50** (0.112g, 0.262mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

$PdCl_2(MeCN)_2$ (0.0097g, 0.0374mmol) and dppp (0.0129g, 0.0313mmol) were dissolved in DMF (1.5mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 4-bromobenzophenone (0.0441g, 0.222mmol). The reaction mixture was then heated at 127°C for 24 hours, before being partitioned between CH_2Cl_2 (5mL) and distilled water (5mL) and then filtered through a hydrophobic frit, which was rinsed with a further 2mL CH_2Cl_2. The combined organics were washed with water (5mL), and filtered through a hydrophobic frit, which was again rinsed with CH_2Cl_2 (2mL). Organics were once more combined and concentrated *in vacuo*. Purification using Silica gel SPE cartridge eluting with petrol → petrol/EtOAc, 97/3 gave 4-acetyl-4'-methyl-biphenyl **72** as a white powder (0.0276g, 0.131mmol, 59%). Analytical data as above.

Cross-coupling using $PdCl_2(MeCN)_2$/dppp catalyst with added water (section 4.3.6.3)



Powdered potassium fluoride (0.0822, 1.41mmol), and distilled water (2 drops) were added to a solution of dichlorotolylgermane **50** (0.0953g, 0.223mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

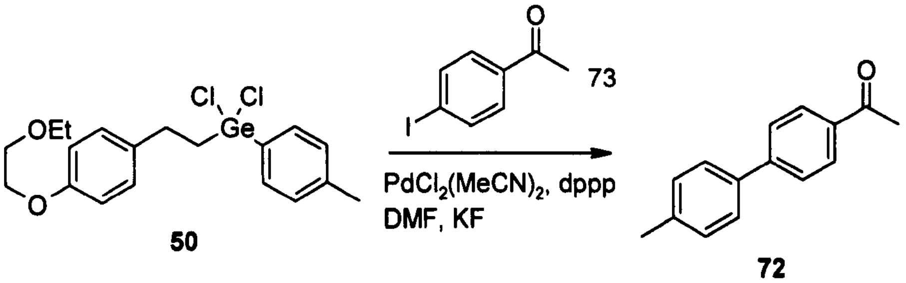
$PdCl_2(MeCN)_2$ (0.0370g, 0.143mmol) and dppp (0.0574g, 0.139mmol) were dissolved in DMF (8mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 4-bromobenzophenone (0.0337g, 0.169mmol). The reaction mixture was then heated at 127°C for 24 hours, before being partitioned between CH_2Cl_2 (5mL) and distilled water (5mL) and then filtered through a hydrophobic frit, which was rinsed with a further 2mL CH_2Cl_2. The combined organics were washed with water (5mL), and filtered through a hydrophobic frit, which was again rinsed with CH_2Cl_2 (2mL). Organics were once more combined and concentrated *in vacuo*. Purification using Silica gel SPE cartridge eluting with petrol → petrol/EtOAc, 97/3 gave 4-acetyl-4'-methyl-biphenyl **72** as a white powder (0.0153g, 0.121mmol, 43%). Analytical data as above.

6.2.4.5 Examples of dichlorotolylgermane (50) cross-coupling using $PdCl_2(MeCN)_2$/dppp catalyst (Figure 4.73)

General method of optimised dichloroarylgermane cross-coupling

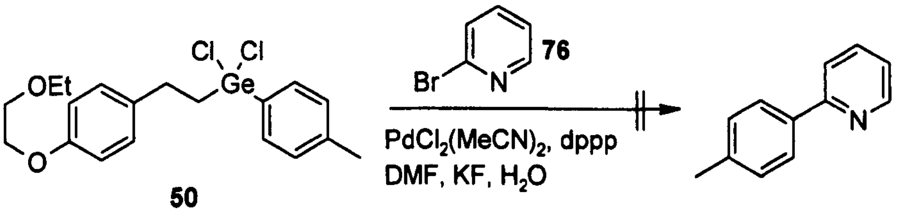
Dichloroarylgermane (Tolyl, or Anisyl) was dissolved in 1mL DMF and stirred with KF for 3 hours at rt to furnish the activated arylgermane. During this time $PdCl_2(MeCN)_2$ and dppp (or IMes·HCl) were dissolved in DMF and stirred at rt for 1 hour to give the active catalytic species. The aryl halide coupling partner and a 1mL portion of the catalyst solution were then added to the arylgermane solution and the resulting mixture heated at 120°C for 24 hours. The crude reaction mixture was partitioned between distilled water (5mL) and CH_2Cl_2 (5mL) and filtered through a hydrophobic frit, which was rinsed with further CH_2Cl_2 (2mL). The combined organics were washed with further water (5mL) and filtered through a second frit, which was again rinsed with CH_2Cl_2 (2mL). The organics were again combined and concentrated *in vacuo* to give the crude reaction mixture.

Cross-coupling with 4-iodoacetophenone (Figure 4.73)



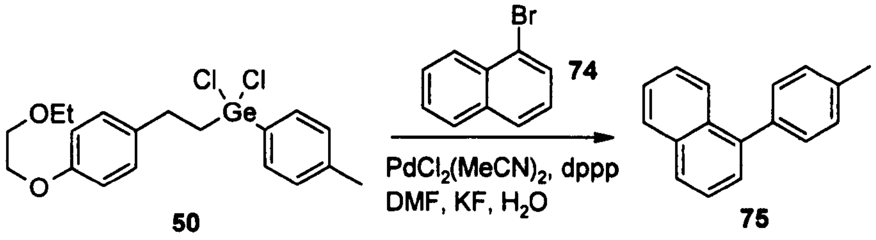
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0798g, 1.37mmol), dichlorotolylgermane **50** (0.0953g, 0.223mmol), 4-iodobenzophenone (0.0427g, 0.174mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0370g, 0.143mmol) and dppp (0.0574g, 0.139mmol) dissolved in DMF (8mL). Purification using Silica gel SPE cartridge eluting with petrol → petrol/EtOAc, 97/3 gave 4-Acetyl-4'-methyl-biphenyl **72** as a white powder (0.0090g, 0.0428mmol, 25%). Analytical data as above.

Cross-coupling with 2-bromopyridine (Figure 4.73)



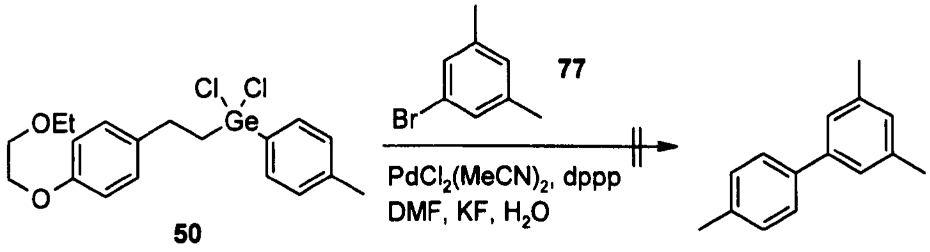
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0817g, 1.41mmol), dichlorotolylgermane **50** (0.0953g, 0.223mmol), 2-bromopyridine (17μL, 0.0282g, 0.178mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0370g, 0.143mmol) and dppp (0.0574g, 0.139mmol) dissolved in DMF (8mL). GC/MS analysis revealed no identifiable products from the reaction.

Cross-coupling with 1-bromonaphthalene (Figure 4.73)



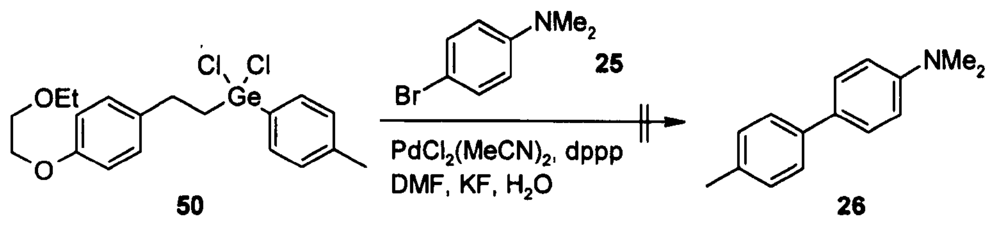
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0806, 1.39mmol), dichlorotolylgermane **50** (0.0953g, 0.223mmol), 1-bromonaphthalene (25μL, 0.0372g, 0.180mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0370g, 0.143mmol) and dppp (0.0574g, 0.139mmol) dissolved in DMF (8mL). Purification using Silica gel SPE cartridge eluting with cyclohexane gave 1-(4-methyl-phenyl)-naphthalene 75[230] as a clear colourless film (0.0311g, 0.142mmol, 79%). **R$_f$** 0.26 (cyclohexane); **^{1}H NMR** ($CDCl_3$) δ 2.48 (3H, s, ArCH_3), 7.31-7.34 (2H, m, Ar CH's), 7.40-7.57 (6H, m, Ar CH's), 7.84-7.96 (3H, m, Ar CH's); **MS** (EI) *m/z* 218 (M^+ 100%), 203 (73%), 189 (11%), 108 (27%), 95 (28%).

Cross-coupling with 5-bromo-meta-xylene (Figure 4.74)



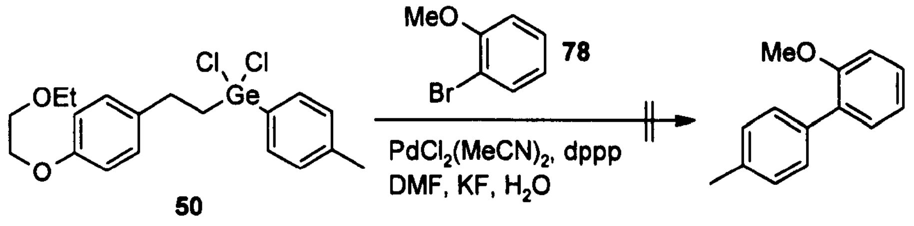
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0810g, 1.39mmol), dichlorotolylgermane **50** (0.0953g, 0.223mmol), 5-bromo-meta-xylene (24μL, 0.0327g, 0.177mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0370g, 0.143mmol) and dppp (0.0574g, 0.139mmol) dissolved in DMF (8mL). GC/MS analysis revealed no identifiable products from the reaction.

Cross-coupling with 4-bromo-N,N-dimethylaniline (Figure 4.74)



Using the general method given above, with the following reagents: powdered potassium fluoride (0.0793g, 1.36mmol), dichlorotolylgermane **50** (0.0953g, 0.223mmol), 4-bromo-*N*,*N*-dimethylaniline (0.0338g, 0.169mmol), and 1mL of PdCl$_2$(MeCN)$_2$ (0.0370g, 0.143mmol) and dppp (0.0574g, 0.139mmol) dissolved in DMF (8mL). GC/MS analysis revealed no identifiable products from the reaction.

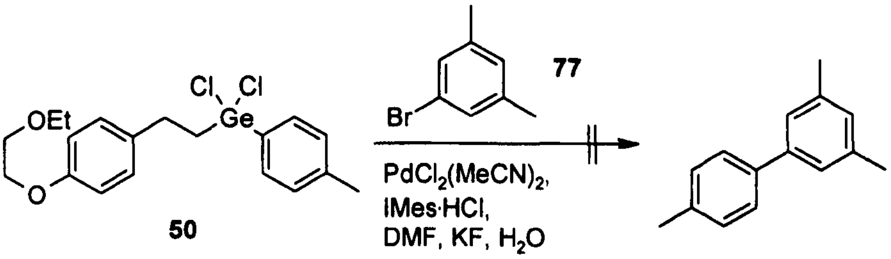
Cross-coupling with 2-bromoanisole (Figure 4.74)



Using the general method given above, with the following reagents: powdered potassium fluoride (0.0859g, 1.48mmol), dichlorotolylgermane **50** (0.0953g, 0.223mmol), 2-bromoanisole (22μL, 0.0330g, 0.176mmol), and 1mL of PdCl$_2$(MeCN)$_2$ (0.0370g, 0.143mmol) and dppp (0.0574g, 0.139mmol) dissolved in DMF (8mL). GC/MS analysis revealed no identifiable products from the reaction.

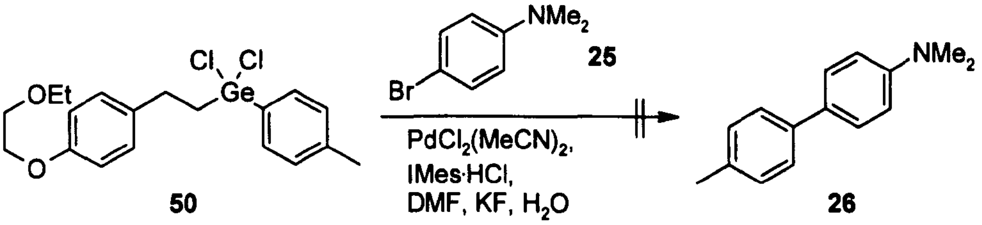
6.2.4.6 Examples of dichlorotolylgermane (50) cross-coupling using $PdCl_2(MeCN)_2$/IMes·HCl catalyst

Cross-coupling with 5-bromo-meta-xylene (Figure 4.74)



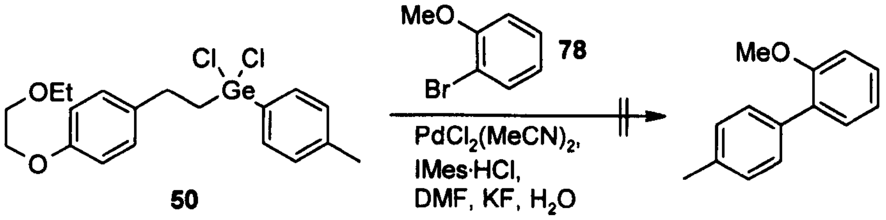
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0917g, 1.58mmol), dichlorotolylgermane **50** (0.0983g, 0.230mmol), 5-bromo-meta-xylene (24μL, 0.0327g, 0.177mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0192g, 0.0740mmol) and IMes·HCl (0.0254g, 0.0745mmol) dissolved in DMF (4mL). GC/MS analysis revealed no identifiable products from the reaction.

Cross-coupling with 4-bromo-N,N-dimethylaniline (Figure 4.74)



Using the general method given above, with the following reagents: powdered potassium fluoride (0.0853g, 1.47mmol), dichlorotolylgermane **50** (0.0983g, 0.230mmol), 4-bromo-*N*,*N*-dimethylaniline (0.0350g, 0.175mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0192g, 0.0740mmol) and IMes·HCl (0.0254g, 0.0745mmol) dissolved in DMF (4mL). GC/MS analysis revealed no identifiable products from the reaction.

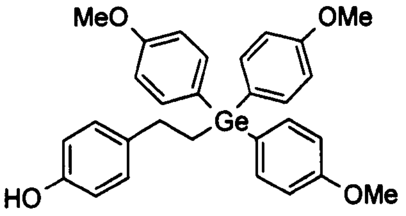
Cross-coupling with 2-bromoanisole (Figure 4.74)



Using the general method given above, with the following reagents: powdered potassium fluoride (0.0818g, 1.41mmol), dichlorotolylgermane **50** (0.0986g, 0.230mmol), 2-bromoanisole (22μL, 0.0330g, 0.177mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0192g, 0.0740mmol) and IMes·HCl (0.0254g, 0.0745mmol) dissolved in DMF (4mL). GC/MS analysis revealed no identifiable products from the reaction.

6.2.4.7 Synthesis of anisylchlorogermanes

4-{2-[Tri-(4-methoxyphenyl)germanyl]ethyl}phenol (79)

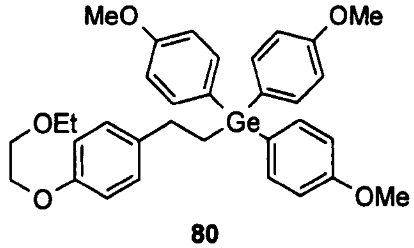


79

Molecular Weight =515.15
Molecular Formula =$C_{29}H_{30}GeO_4$

4-Bromoanisole (7.5mL, 11.2g, 0.0599mol) was added to a suspension of magnesium turnings (1.54g, 0.0632mol) in THF (130mL), and the resulting solution stirred until it had cooled to rt. A solution of trichlorogermylphenol **8** (3.00g, 10.0mmol) dissolved in anhydrous THF (20mL) was then added to the Grignard reagent and heated at reflux for 17.5hours. The reaction mixture was quenched with methanol (20mL) and then partitioned between distilled water (100mL) and EtOAc (3 × 100mL). Acid was not used in the work-up to avoid cleavage of the germanium-aryl bonds. The organic washings were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification with a SPE cartridge (50g, eluting with petrol → petrol/EtOAc, 19/1 → petrol/EtOAc, 9/1 → petrol/EtOAc, 8/2 → petrol/EtOAc, 7/3) gave trianisylphenol **79** as a clear colourless oil (3.82g, 7.42mmol, 74%). **R*f*** 0.21 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 1.77 (2H, m, $CH_2C\mathit{H}_2Ge$), 2.76 (2H, m, $C\mathit{H}_2CH_2Ge$), 3.84 (9H, s, $ArOC\mathit{H}_3$), 6.74 (2H, d, *J* 8.0, $HOCC\mathit{H}CHCCH_2$), 6.95 (6H, d, *J* 8.5, $GeCCHC\mathit{H}COCH_3$), 7.05 (2H, d, *J* 8.0, $HOCCHC\mathit{H}CCH_2$), 7.41 (6H, d, *J* 8.5, $GeCC\mathit{H}CHCOCH_3$); **^{13}C NMR** ($CDCl_3$) δ 16.7 (t), 30.3 (t), 55.1 (q), 114.0 (d), 115.2 (d), 128.2 (s), 128.9 (d), 136.2 (d), 137.0 (s), 153.6 (s), 160.3 (s); **IR** (neat) 3417, 2931, 1592, 1498, 1279, 1246, 1179, 1091, 1029, 816, 793cm^{-1}; **MS** (EI) *m/z* 516 (M^+ 1%), 395 (100%), 347 (13%), 271 (18%), 181 (17%), 120 (17%), 107 (16%), 91 (31%); **HRMS** calc'd for $C_{29}H_{30}{}^{74}GeO_4$ 516.1356, found 516.1358, error -0.3ppm; **Elemental analysis** expected for $C_{21}H_{30}GeO_2$ C 67.72%, H 5.87%, analysis found C 67.41%, H 5.78%.

4-{2-[Tri-(4-methoxyphenyl)germanyl]ethyl}phenyl 2-ethoxy-ethyl ether (80)



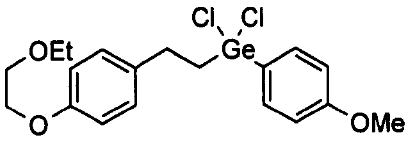
80

Molecular Weight =587.26
Molecular Formula =$C_{33}H_{38}GeO_5$

Cesium carbonate (2.17g, 6.65mmol), TBAI (0.157g, 0.42mmol), and 2-chloroethyl ethyl ether (2.5mL, 2.47g, 22.8mmol) were added to a solution of trianisylphenol **79** (2.33g, 4.52mmol) dissolved in MeCN (75mL), and the resulting solution heated at reflux for 15 hours. Once the reaction was complete by TLC analysis the mixture was partitioned between distilled water (100mL) and EtOAc (2 × 100mL, 50mL). The combined organic washings were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then filtered through silica (5g SPE cartridge, eluted with petrol/EtOAc, 9/1), before being concentrated to give trianisylgermane **80** as a pale yellow oil (2.06g, 3.51mmol, 78%). **R*f*** 0.44 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 1.25 (3H, t, *J* 7.0, $C\mathit{H}_3CH_2O$), 1.76 (2H, m, $CH_2C\mathit{H}_2Ge$), 2.75 (2H, m, $C\mathit{H}_2CH_2Ge$), 3.61 (2H, q, *J* 7.0, $CH_3C\mathit{H}_2O$), 3.79 (2H, t, *J* 5.0, $OC\mathit{H}_2CH_2OAr$), 3.83 (9H, s, $ArOC\mathit{H}_3$), 4.10 (2H, t, *J* 5.0, $OCH_2C\mathit{H}_2OAr$), 6.83

(2H, d, *J* 8.5, OCC*H*CHCCH$_2$), 6.93 (6H, d, *J* 8.5, GeCCHC*H*COCH$_3$), 7.08 (2H, d, *J* 8.5, OCCHC*H*CCH$_2$), 7.40 (6H, d, *J* 8.5, GeCC*H*CHCOCH$_3$); **^{13}C NMR** (CDCl$_3$) δ 15.2 (q), 16.7 (t), 30.3 (t), 55.1 (q), 66.8 (t), 67.5 (t), 69.0 (t), 114.0 (d), 114.6 (d), 128.2 (s), 128.7 (d), 136.1 (d), 137.1 (s), 153.6 (s), 160.3 (s); **IR** (neat) 2929, 1592, 1511, 1290, 1253, 1181, 1094, 1027, 823cm^{-1}; **MS** (EI) *m/z* 588 (M^{+} 2%), 480 (8%), 395 (100%), 347 (16%), 271 (66%), 181 (31%), 91 (46%); **HRMS** calc'd for $C_{33}H_{38}{}^{74}GeO_5$ 588.1931, found 588.1939, error −1.4ppm; **Elemental** $C_{33}H_{38}GeO_5$ expected C 67.5%, H 6.5%, found C 67.1%, H 6.6%.

4-{2-[Dichloro-(4-methoxy-phenyl)-germanyl]-ethyl}-phenyl 2-ethoxy-ethyl ether (81)



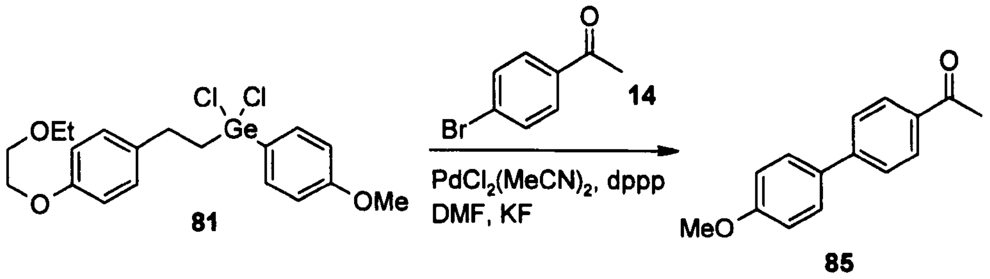
81

Molecular Weight =443.90
Molecular Formula =$C_{19}H_{24}Cl_2GeO_3$

Trianisylgermane **80** (2.04g, 3.47mmol) was dissolved in CH$_2$Cl$_2$ (27mL). To the resulting solution aqueous HCl (1M, 4.5mL, 4.5mmol) was added dropwise over 2 minutes with vigorous stirring. After 5 minutes, c.HCl (53mL, 0.530mol) was added, dropwise to begin with, to give a vivid violet coloured organic layer. The resulting biphasic mixture was vigorously stirred at rt for 45 minutes, whereupon the organic layer was pipetted out and filtered through a hydrophobic frit. The acid layer was shaken with further CH$_2$Cl$_2$ (2 × 20mL), which was also removed and filtered through a hydrophobic frit, and the combined organic washings concentrated *in vacuo*, with further volatiles removed under a high vacuum. Proton NMR analysis of the resulting crude product (1.39g) revealed a *ca.* 50/50 mixture of 4-{2-[chloro-di-(4-methoxy-phenyl)-germanyl]-ethyl}-phenyl 2-ethoxy-ethyl ether and dichloroanisylgermane **81**. The crude reaction mixture was redissolved in CH$_2$Cl$_2$ (20mL), further c.HCl (50mL, 0.500mol) added and the solution again vigorously stirred for 2 hours. The CH$_2$Cl$_2$ layer was again removed, the acid layer washed CH$_2$Cl$_2$ (2 × 20mL) and the combined washings again filtered through a hydrophobic frit, before being concentrated *in vacuo* and further volatiles removed under a high vacuum to give dichloroanisylgermane **81** as a pale brown oil (1.27g, 2.86mmol, 82%). **R_f** 0.00 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 1.26 (3H, t, *J* 7.0, CH_3CH_2O), 2.09 (2H, m, CH_2CH_2Ge), 2.96 (2H, m, CH_2CH_2Ge), 3.61 (2H, q, *J* 7.0, CH_3CH_2O), 3.79 (2H, t, *J* 5.0, OCH_2CH_2OAr), 3.85 (3H, s, $ArOCH_3$), 4.10 (2H, t, *J* 5.0, OCH_2CH_2OAr), 6.84 (2H, d, *J* 8.5, $OCCHCHCCH_2$), 6.97 (2H, d, *J* 8.5, $GeCCHCHCOCH_3$), 7.11 (2H, d, *J* 8.5, $OCCHCHCCH_2$), 7.49 (2H, d, *J* 8.5, $GeCCHCHCOCH_3$); **^{13}C NMR** ($CDCl_3$) δ 15.2 (q), 27.8 (t), 28.6 (t), 55.3 (q), 66.9 (t), 67.5 (t), 69.0 (t), 114.5 (d), 114.8 (d), 126.5 (s), 129.0 (d), 133.7 (d), 157.5 (s), 162.2 (s), one quaternary carbon not observed; **IR** (neat) 2930, 1592, 1512, 1290, 1253, 1181, 1094, 1027, 824, 795cm^{-1}; **MS** (EI) *m/z* 444 (M^{+} 18%), 251 (5%), 192 (68%), 120 (41%), 107 (100%), 92 (74%), 78 (46%), 45 (78%); **HRMS** calc'd for $C_{19}H_{24}Cl_2{}^{74}GeO_3$ 444.0314, found 444.0302, error 2.9ppm.

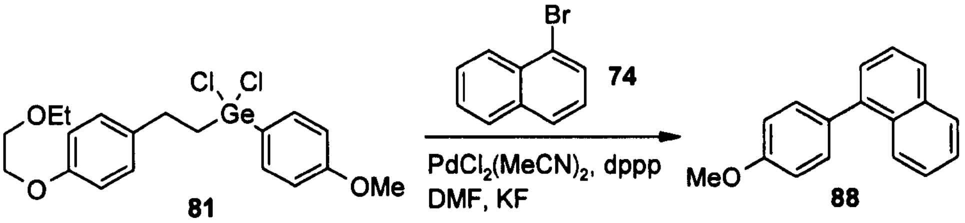
6.2.4.8 Cross-coupling of anisyldichlorogermane (81) (Figure 4.77)

Cross-coupling with 4-bromo-acetophenone



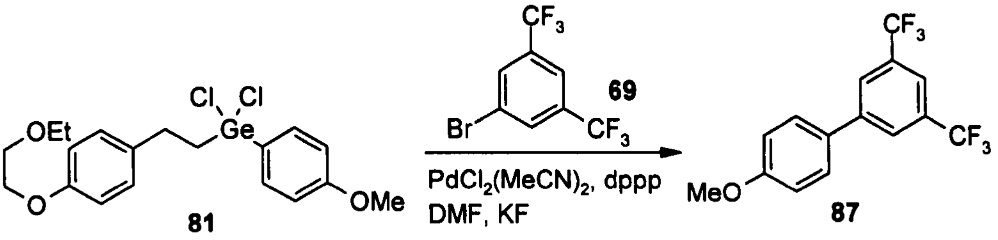
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0913g, 1.57mmol), dichloroanisylgermane **81** (0.118g, 0.266mmol), and 4-bromobenzophenone (0.0384g, 0.193mmol). $PdCl_2(MeCN)_2$ (0.0232g, 0.0894mmol) and dppp (0.0348g, 0.0844mmol) were dissolved in DMF (4mL). Purification using Silica gel SPE cartridge eluting with petrol → petrol/EtOAc, 97/3 gave 4-acetyl-4'-methoxy biphenyl **85**[213] as a colourless film (0.0021g, 0.0100mmol, 5%). **R_f** 0.08 (cyclohexane); **^{1}H NMR** ($CDCl_3$) δ 2.62 (3H, s, $ArCOCH_3$), 3.85 (3H, s, $ArOCH_3$), 6.97 (2H, m, $CH_3OCCHCHCAr$), 7.45-7.50 (4H, m, $CH_3OCCHCHCCCHCHCCOCH_3$), 7.98 (2H, m, $ArCCHCHCCOCH_3$); **MS** *m/z* (EI) 226 (M^{+} 53%), 211 (100%), 183 (20%), 168 (28%), 139 (43%), 106 (14%).

Cross-coupling with 1-bromonaphthalene



Using the general method given above, with the following reagents: powdered potassium fluoride (0.0834g, 1.44mmol), dichloroanisylgermane **81** (0.115g, 0.259mmol), 1-bromonaphthalene (28μL, 0.0417g, 0.201mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0160g, 0.0617mmol) and dppp (0.0245g, 0.0594mmol) dissolved in DMF (3mL). Purification using Silica gel SPE cartridge eluting with petrol → petrol/EtOAc, 19/1 gave 1-(4-methoxy-phenyl)-naphthalene **88**[231] as clear colourless prisms (0.0272g, 0.116mmol, 58%). **R_f** 0.16 (cyclohexane); **^{1}H NMR** ($CDCl_3$) δ 3.91 (3H, s, ArOCH_3), 7.01-7.07 (2H, m, Ar CH's), 7.40-7.56 (6H, m, Ar CH's), 7.84-7.96 (3H, m, Ar CH's); **MS** *m/z* (EI) 234 (M^+ 100%), 219 (38%), 203 (14%), 189 (55%), 163 (9%), 101 (23%), 95 (29%); **Melting point** 110.4-116.2°C (*cf.* 114-115°C[232]).

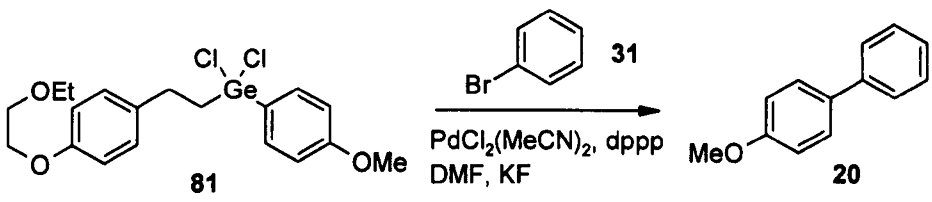
Cross-coupling with 3,5-bis(trifluoromethyl)bromobenzene



Using the general method given above, with the following reagents: powdered potassium fluoride (0.0863g, 1.49mmol) dichloroanisylgermane **81** (0.114g, 0.257mmol), 3,5-bis-trifluoromethyl-bromo-benzene (34μL, 0.0578g, 0.197mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0160g, 0.0617mmol) and dppp (0.0245g, 0.0594mmol) dissolved in DMF (3mL). Purification using Silica gel SPE cartridge eluting with cyclohexane gave 4-methoxy-3',5'-bis-trifluoromethyl-biphenyl **87** as a clear colourless oil (0.0451g, 0.141mmol, 71%). **R_f** 0.22 (cyclohexane); **^{1}H NMR**

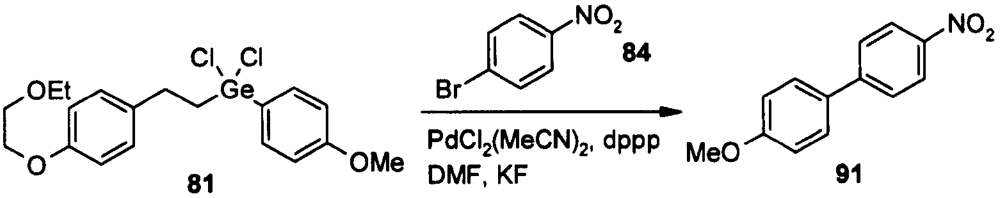
($CDCl_3$) δ 3.89 (3H, s, $\mathrm{ArOC}\mathit{H}_3$), 7.04 (2H, d, *J* 9.0, $\mathrm{CH_3OCC}\mathit{H}\mathrm{CHCAr}$), 7.57 (2H, d, *J* 9.0, $\mathrm{CH_3OCCHC}\mathit{H}\mathrm{CAr}$), 7.81 (1H, s, $\mathrm{CF_3CC}\mathit{H}\mathrm{CCF_3}$), 7.98 (2H, s, $\mathrm{ArCC}\mathit{H}\mathrm{CCF_3}$); ^{13}**C NMR** ($CDCl_3$) δ 55.4 (q), 114.7 (d), 120.2 (d), 126.6 (d), 128.4 (d), 5 quaternary carbons not seen; **IR** (neat) 2940, 2842, 1610, 1521, 1383, 1279, 1185, 1132, 1061, 830, 682cm^{-1}; **MS** (EI) *m/z* 320 (M^{+} 100%), 305 (16%), 301 (20%), 277 (60%), 251 (9%), 188 (13%); **HRMS** calc'd for $C_{15}H_{10}F_6$ O 320.0636, found 320.0625, error 3.4ppm.

Cross-coupling with bromobenzene



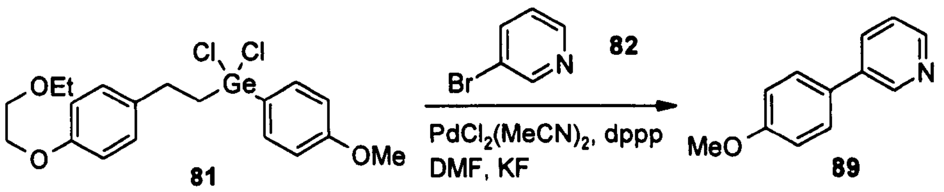
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0889g, 1.53mmol), dichloroanisylgermane **81** (0.0997g, 0.225mmol), bromobenzene (20μL, 0.0298g, 0.190mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0277g, 0.107mmol) and dppp (0.0448g, 0.109mmol) dissolved in DMF (5mL). Purification using Silica gel SPE cartridge eluting with cyclohexane gave 4-methoxy-biphenyl **20**[217] as a white powder (0.0125g, 0.0678mmol, 36%). **R$_f$** 0.26 (cyclohexane); ^{1}**H NMR** ($CDCl_3$) δ 3.87 (3H, s, $\mathrm{ArOC}\mathit{H}_3$), 6.98-7.01 (2H, m, $\mathrm{CH_3OCC}\mathit{H}\mathrm{CHCAr}$), 7.31-7.34 (1H, m, $\mathrm{ArCCHCHC}\mathit{H}$), 7.40-7.46 (2H, m, Ar CH's), 7.53-7.59 (4H, m, Ar CH's); **MS** (EI) *m/z* 184 (M^{+} 100%), 169 (57%), 141 (57%), 115 (46%), 76 (8%); **Melting point** 86.7-88.2°C (*cf.* 87°C[233]).

Cross-coupling with 4-nitrobromobenzene



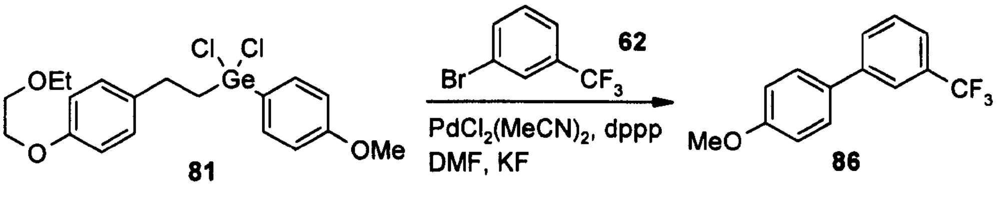
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0886g, 1.52mmol), dichloroanisylgermane **81** (0.0970g, 0.219mmol), 4-nitrobromobenzene (0.0392g, 0.194mmol), and 1mL of PdCl$_2$(MeCN)$_2$ (0.0277g, 0.107mmol) and dppp (0.0448g, 0.109mmol) dissolved in DMF (5mL). Purification using Silica gel SPE cartridge eluting with cyclohexane → petrol/EtOAc, 97/3 gave 4-methoxy-4'nitro-biphenyl **91**[234] as a yellow amorphous powder (0.0217g, 0.0947mmol, 47%). **R**$_f$ 0.35 (Petrol/EtOAc, 9/1); ^{1}**H NMR** (CDCl$_3$) δ 3.89 (3H, s, ArOC*H*$_3$), 7.03 (2H, *J* 9.0, CH$_3$OCC*H*CHCAr), 7.59 (2H, *J* 9.0, CH$_3$OCCHC*H*CAr), 7.70 (2H, *J* 9.0, ArCC*H*CHCNO$_2$), 8.28 (2H, *J* 9.0, ArCCHC*H*CNO$_2$); **MS** (EI) *m/z* 229 (M$^+$ 100%), 199 (27%), 183 (18%), 168 (32%), 152 (22%), 139 (64%); **Melting point** 105.6-106.7°C (*cf.* 107-108°C[98]).

Cross-coupling with 3-bromopyridine



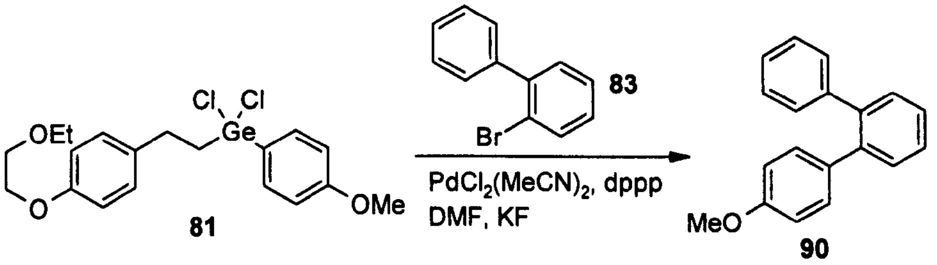
Using the general method given above, with the following reagents: powdered potassium fluoride (0.0887g, 1.53mmol), dichloroanisylgermane **81** (0.0963g, 0.217mmol), 3-bromopyridine (18μL, 0.0291g, 0.184mmol), and 1mL of PdCl$_2$(MeCN)$_2$ (0.0277g, 0.107mmol) and dppp (0.0448g, 0.109mmol) dissolved in DMF (5mL). Purification using Silica gel SPE cartridge eluting with cyclohexane → petrol/EtOAc, 9/1 gave 3-(4-methoxy-phenyl)-pyridine **89**[235] as an off white film (0.0150g, 0.0810mmol, 44%). **R**$_f$ 0.13 (Petrol/EtOAc, 8/2); ^{1}**H NMR** (CDCl$_3$) δ 3.87 (3H, s, ArOC*H*$_3$), 7.02 (2H, d, *J* 9.0, CH$_3$OCC*H*CHCAr), 7.35 (1H, dd, *J* 5.0, *J* 8.0, ArCCHC*H*CHN), 7.53 (2H, d, *J* 9.0, CH_3OCCHC*H*CAr), 7.85 (1H, d, *J* 8.0, ArCC*H*CHCHN), 8.55 (1H, d, *J* 5.0, ArCCHCHC*H*N), 8.83 (1H, s, ArCC*H*N); **MS** (EI) *m/z* 185 (M^{+} 100%), 170 (55%), 142 (50%), 115 (27%), 89 (17%), 89 (17%).

Cross-coupling with 3-bromobenzotrifluoride



Using the general method given above, with the following reagents: powdered potassium fluoride (0.0872g, 1.50mmol), dichloroanisylgermane **81** (0.0971g, 0.219mmol), 3-bromobenzotrifluoride (26μL, 0.0424g, 0.188mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0277g, 0.107mmol) and dppp (0.0448g, 0.109mmol) dissolved in DMF (5mL). Purification using Silica gel SPE cartridge eluting with cyclohexane gave 4-methoxy-3'-trifluoromethyl-biphenyl **86** as a clear colourless oil[236] (0.0246g, 0.0975mmol, 52%): **R**$_f$ 0.27 (cyclohexane); ^{1}**H NMR** ($CDCl_3$) δ 3.87 (3H, s, ArOC*H*$_3$), 6.98-7.02 (2H, m, CH_3OCC*H*CHCAr), 7.52-7.56 (4H, m, Ar CH's), 7.71-7.74 (1H, m, Ar CH), 7.79 (1H, s, ArCC*H*CCF$_3$); **MS** (EI) *m/z* 252 (M^{+} 100%), 237 (41%), 209 (69%), 183 (17%), 139 (15%).

Cross-coupling with 2-bromo-biphenyl



Using the general method given above, with the following reagents: powdered potassium fluoride (0.0834g, 1.44mmol), dichloroanisylgermane **81** (0.0941g, 0.212mmol), 2-bromo-biphenyl (32μL, 0.0440g, 0.189mmol), and 1mL of $PdCl_2(MeCN)_2$ (0.0277g, 0.107mmol) and dppp (0.0448g, 0.109mmol) dissolved in

DMF (5mL). Purification using Silica gel SPE cartridge eluting with cyclohexane gave:

2-Bromobiphenyl starting material as a clear colourless liquid (0.0183g, 0.0786mmol, 42%). **R$_f$ 0.57** (cyclohexane); **^{1}H NMR** (CDCl$_3$) δ 7.17-7.24 (1H, m, Ar CH), 7.32-7.37 (2H, m, Ar CH's), 7.42 (5H, m, Ar CH's), 7.66-7.69 (1H, m, Ar CH); **MS** (EI) *m/z* 232 (M^{+} 72%), 152 (100%), 126 (11%), 76 (42%).

A complex mixture of inseparable products (0.0152g), GC/MS indicated the presence of:

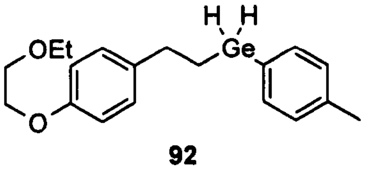
4,4'-Dimethoxybiphenyl **R$_t$** 16.74min; **MS** (EI) *m/z* 214 (M^{+} 99%), 199 (100%), 171 (43%), 156 (15%), 139 (13%), 128 (28%).

4''-Methoxy-[1,1';2',1'']terphenyl **90**[226] **R$_t$** 18.73min; **MS** (EI) *m/z* 260 (M^{+} 100%), 245 (14%), 229 (41%), 215 (46%), 202 (41%), 107 (17%), 95 (21%).

[1,1';2',1'';2'',1''']Quaterphenyl **R$_t$** 21.38min; **MS** (EI) *m/z* 304 (M^{+} 100%), 289 (11%), 276 (7%), 226 (8%), 151 (48%), 145 (27%).

6.2.5 Approaches towards Hydridogermane cross-coupling

4-{2-[(4-Methyl-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether (92)

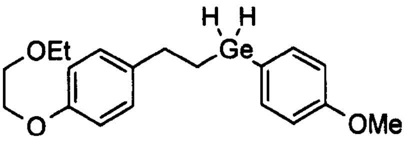


92

Molecular Weight =359.01
Molecular Formula =$C_{19}H_{26}GeO_2$

LiAlH$_4$ (0.0756g, 1.98mmol) was added to a solution of dichlorotolylgermane **50** (0.109g, 0.254mmol) in anhydrous THF (10mL) at 0°C, the solution was then warmed to rt before being heated at reflux for 16.5 hours. The crude reaction mixture was cooled to 0°C before aqueous HCl (1M, 1mL) was added cautiously. Once effervescence had ceased, further aqueous HCl was added (1M, 25mL) and the acid layer extracted with CH$_2$Cl$_2$ (2 × 25mL). The organics were combined and washed with HCl (1M, 10mL), before being dried with $MgSO_4$, filtered and concentrated *in vacuo* to give dihydrotolylgermane **92** as a clear colourless oil (0.0911g, 100%); $\mathbf{R}_f$ 0.71 (petrol/EtOAc, 9/1); ^{1}**H NMR** ($CDCl_3$) δ 1.26 (3H, t, *J* 7.0, CH_3CH_2O), 1.47 (2H, m, CH_2CH_2Ge), 2.36 (3H, s, $ArCH_3$), 2.76 (2H, m, CH_2CH_2Ge), 3.61 (2H, q, *J* 7.0, CH_3CH_2O), 3.79 (2H, t, *J* 5.0, OCH_2CH_2OAr), 4.11 (2H, t, *J* 5.0, OCH_2CH_2OAr), 4.36 (2H, m, GeH_2), 6.85 (2H, d, *J* 9.0, $OCCHCHCCH_2$), 7.09 (2H, d, *J* 9.0, $OCCHCHCCH_2$), 7.17 (2H, d, *J* 8.0, $GeCCHCHCCH_3$), 7.38 (2H, d, *J* 8.0, $GeCCHCHCCH_3$); ^{13}**C NMR** ($CDCl_3$) δ 13.8 (t), 15.2 (q), 21.4 (q), 31.8 (t), 66.9 (t), 67.5 (t), 69.0 (t), 114.6 (d), 128.8 (d), 129.1 (d), 131.1 (s), 134.9 (d), 136.2 (s), 138.6 (s), 157.1 (s); **IR** (neat) 2922, 2043, 1511, 1245, 1124, 747 cm^{-1}; **MS** (EI) *m/z* 360 ($M^{\cdot+}$ 18%), 260 (8%), 239 (13%), 165 (47%), 120 (55%), 91 (43%), 73 (49%), 45 (100%); **HRMS** calc'd for $C_{19}H_{26}{}^{74}GeO_2$ 360.1145, found 360.1143, error 0.5ppm.

4-{2-[(4-Methoxy-phenyl)-germanyl]-ethyl}-phenyl (2-ethoxy-ethyl) ether (93)



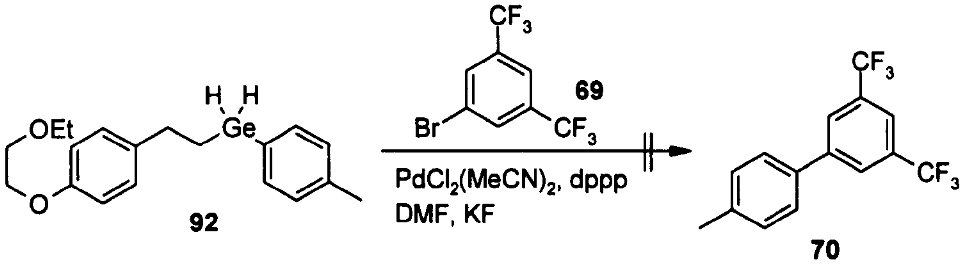
Molecular Weight =375.01
Molecular Formula =$C_{19}H_{26}GeO_3$

93

$LiAlH_4$ (0.101g, 2.65mmol) was added to a solution of dichloroanisylgermane **81** (0.149g, 0.336mmol) in anhydrous THF (10mL) at 0°C, the solution was then warmed to rt before being heated at reflux for 17 hours. The crude reaction mixture was cooled to 0°C before saturated aqueous NH_4Cl solution (1mL) was added cautiously. Once effervescence had ceased, further saturated aqueous NH_4Cl was added (25mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 25mL). The organics were combined filtered through a hydrophobic frit, before being concentrated *in vacuo* to give dihydroanisylgermane **93** as a clear colourless oil (0.115g, 0.307mmol, 91%); $\mathbf{R}_f$ 0.07 (petrol/EtOAc, 9/1); ^{1}**H NMR** ($CDCl_3$) δ 1.27 (3H, t, *J* 7.0, CH_3CH_2O), 1.43-1.52 (2H, m, CH_2CH_2Ge), 2.74-2.80 (2H, m, CH_2CH_2Ge), 3.62 (2H, q, *J* 7.0, CH_3CH_2O), 3.80 (2H, t, *J* 5.0, OCH_2CH_2OAr), 3.83 (3H, s, $ArOCH_3$), 4.12 (2H, t, *J* 5.0, OCH_2CH_2OAr), 4.37 (2H, m, GeH_2), 6.86 (2H, d, *J* 9.0, $OCCHCHCCH_2$), 6.92

(2H, d, *J* 9.0, GeCCHC*H*COCH$_3$), 7.11 (2H, d, *J* 9.0, OCCHC*H*CCH$_2$), 7.41 (2H, d, *J* 9.0, GeCC*H*CHCOCH$_3$); **^{13}C NMR** (CDCl$_3$) δ 13.9 (t), 15.2 (q), 31.8 (t), 55.1 (q), 66.9 (t), 67.5 (t), 69.0 (t), 114.0 (d), 114.5 (d), 128.8 (d), 136.2 (d), 157.0 (s), 176.1 (s), two quaternary carbons not observed; **IR** (neat) 2974, 2928, 2870, 2043, 1593, 1511, 1247, 1180, 1125, 823 cm^{-1}; **MS** (EI) *m/z* 376 (M$^+$ 10%), 268 (16%), 239 (22%), 192 (35%), 181 (39%), 121 (27%), 73 (36%), 45 (100%); **HRMS** calc'd for $C_{19}H_{26}{}^{74}GeO_3$ 376.1094, found 376.1102, error –2.2ppm.

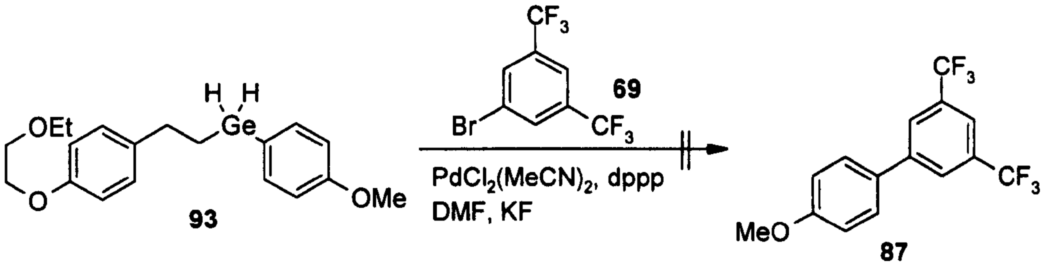
Cross-coupling of dihydrotolylgermane (92)



Powdered potassium fluoride (0.0872g, 1.50mmol), was added to a solution of dihydrotolylgermane **92** (0.0842g, 0.235mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

PdCl$_2$(MeCN)$_2$ (0.0136g, 0.0524mmol) and dppp (0.0208g, 0.0504mmol) were dissolved in DMF (2.5mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bistrifluoromethylbromobenzene (35μL, 0.0594g, 0.203mmol). The reaction mixture was then heated at 127°C for 22 hours, before being partitioned between CH$_2$Cl$_2$ (5mL) and distilled water (5mL) and then filtered through a hydrophobic frit, which was rinsed with a further 2mL CH$_2$Cl$_2$. The combined organics were washed with water (5mL), and filtered through a hydrophobic frit, which was again rinsed with CH$_2$Cl$_2$ (2mL). Organics were once more combined and concentrated *in vacuo*. GC/MS analysis revealed the presence of no identifiable products.

Cross-coupling of dihydroanisylgermane (93)



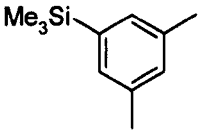
Powdered potassium fluoride (0.103g, 1.77mmol), was added to a solution of dihydroanisylgermane **93** (0.108g, 0.275mmol) dissolved in DMF (1mL), and then stirred at rt for 3 hours.

$PdCl_2(MeCN)_2$ (0.0136g, 0.0524mmol) and dppp (0.0208g, 0.0504mmol) were dissolved in DMF (2.5mL) and stirred at rt for 1 hour. 1mL of the resulting catalyst solution was then added to the solution of hydrolysed chlorogermane, along with 3,5-bistrifluoromethylbromobenzene (35μL, 0.0594g, 0.203mmol). The reaction mixture was then heated at 127°C for 22 hours, before being partitioned between CH_2Cl_2 (5mL) and distilled water (5mL) and then filtered through a hydrophobic frit, which was rinsed with a further 2mL CH_2Cl_2. The combined organics were washed with water (5mL), and filtered through a hydrophobic frit, which was again rinsed with CH_2Cl_2 (2mL). Organics were once more combined and concentrated *in vacuo*. GC/MS analysis revealed the presence of no identifiable products.

6.3 Friedel-Crafts degermylation

6.3.1 Synthesis

Trimethyl-(3,5-dimethyl-phenyl)-silane (94)[202]

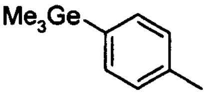


94

Molecular Weight =178.35
Molecular Formula =$C_{11}H_{18}Si$

3,5-Dimethylbromobenzene (0.4mL, 0.545g, 2.94mmol) was dissolved in anhydrous THF (20mL) and cooled to -78°C. s-BuLi (1.3M, 3.17mL, 4.12mmol) was added slowly and dropwise, and the resulting solution stirred for 30 minutes. TMS-Cl (0.190mL, 0.163g, 1.50mmol) was then added dropwise and the solution stirred for 30 minutes, and then allowed to warm to rt over 1 hour. Distilled water (5mL) was added dropwise and the resulting mixture was partitioned between EtOAc (2 × 25mL) and 1m HCl (20mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (5 × 7cm Silica gel, eluting with petrol) gave Silylxylene **94** as a clear colourless liquid (0.182g, 1.02mmol, 68%). **R*f*** 0.90 (petrol); **^{1}H NMR** ($CDCl_3$) δ 0.35 (9H, s, (C*H*$_3$)$_3$Si), 2.42 (6H, s, C*H*$_3$C), 7.10 (1H, s, CH_3CC*H*CCH_3), 7.24 (2H, s, C*H*C(Si(CH_3)$_3$)C*H*); **MS** *m/z* (EI) 178 (M^+ 29%), 163 (100%), 135 (21%), 105 (15%).

Trimethyl-(4-methyl-phenyl)-germane (41)[221]

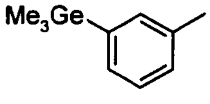


41

Molecular Weight =208.83
Molecular Formula =$C_{10}H_{16}Ge$

Trimethylgermanium bromide (1.7mL, 2.62g, 13.3mmol) was dissolved in anhydrous THF (20mL) under N_2 and cooled to 0°C. *p*-TolMgBr (1.0M in THF, 11mL, 11mmol) was added dropwise and the mixture stirred at rt for 4.5 hours before being quenched with distilled water (2mL). The resulting mixture was partitioned between 1M HCl (20mL) and Et_2O (3 × 20mL) before being dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification using a 50g Silica gel SPE cartridge eluting with petrol gave *p*-tolylgermane **41** as a clear colourless liquid (2.08g, 9.96mmol, 91%). **R*f*** 0.80 (petrol); **^{1}H NMR** ($CDCl_3$) δ 0.40 (9H, s, (C*H*$_3$)$_3$Ge), 2.37 (3H, s, C*H*$_3$C), 7.21 (2H, d, *J* 7.0, C*H*(CH_3)CC*H*), 7.41 (2H, d, *J* 7.0, C*H*C(Ge(CH_3)$_3$)C*H*); **MS** *m/z* (EI) 210 (M^+ 5%), 195 (100%), 165 (25%), 139 (9%), 105 (20%), 91 (39%).

Trimethyl-(3-methylphenyl)-germane (104)[237,238]

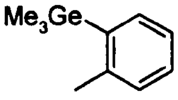


104

Molecular Weight =208.83
Molecular Formula =$C_{10}H_{16}Ge$

3-Bromotoluene (0.370mL, 0.522g, 3.05mmol) was dissolved in anhydrous THF (14mL) under N_2 and cooled to -78°C. n-BuLi (2.5M, 1.8mL, 4.50mmol) was added slowly and dropwise and the resulting solution stirred for 25 minutes. Trimethylgermanium bromide (0.490mL, 0.757g, 3.83mmol) was then added dropwise and the reaction mixture stirred for 30 minutes. The CO_2/acetone bath was removed, and the reaction mixture stirred for a further 20 minutes before being quenched with distilled water (2mL) and partitioned between Et_2O (2 × 20mL) and H_2O (20mL). The organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. GC/MS of the crude reaction mixture indicated the presence of a significant amount of unreacted aryl bromide. The crude mixture was dissolved in THF (14mL) and exposed to n-BuLi (1.0mL, 2.5M, 2.5mmol) at -78°C for 30 minutes, before being quenched for a second time with trimethylgermanium bromide (0.490mL, 0.757g, 3.83mmol) and stirred for a further 15 minutes. Work up as before gave a crude mixture. Purification by column chromatography (4 × 2cm Silica gel, eluting with petrol) gave *m*-tolylgermane **104** as a clear colourless liquid (0.0742g, 0.355mmol, 12%). **R*f*** 0.74 (petrol); **^{1}H NMR** ($CDCl_3$) δ 0.38 (9H, s, (CH_3)$_3$Ge), 2.35 (3H, s, CH_3C), 7.12-7.29 (4H, m, Ar C*H*'s); **MS** *m/z* (EI) 210 (M^+ 5%), 195 (100%), 165 (20%), 105 (11%), 91 (45%).

Trimethyl-(2-methylphenyl)-germane (103)[237,238]



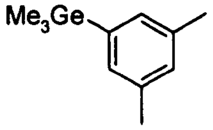
103

Molecular Weight =208.83
Molecular Formula =$C_{10}H_{16}Ge$

2-Bromotoluene (0.360mL, 0.512g, 2.99mmol) was dissolved in anhydrous THF (15mL) under N_2 and cooled to -78°C. s-BuLi (1.3M, 3.5mL, 4.55mmol) was added slowly and dropwise and the resulting solution stirred for 5 minutes.

Trimethylgermanium bromide (0.485mL, 0.749g, 3.79mmol) was then added dropwise and the reaction mixture stirred for 15 minutes. The CO_2/acetone bath was removed, and the reaction mixture stirred for a further 15 minutes before being quenched with distilled water (2mL) and partitioned between Et_2O (2 × 20mL) and H_2O (20mL). The organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The resulting mixture was purified by column chromatography (4 × 2cm Silica gel, eluting with petrol) to give *o*-tolylgermane **103** as a clear colourless liquid (0.450g, 2.16mmol, 72%). **R*f*** 0.83 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 0.46 (9H, s, $(CH_3)_3Ge$), 2.46 (3H, s, CH_3C), 7.18-7.27 (3H, m, Ar C*H*'s), 7.42-7.46 (1H, m, $(CH_3)_3GeCCH$); **MS** *m/z* (EI) 210 (M^+ 8%), 195 (64%), 165 (15%), 105 (25%), 91 (100%).

Trimethyl-(3,5-dimethyl-phenyl)-germane (105)

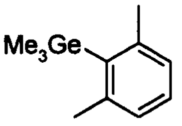


105

Molecular Weight =222.86
Molecular Formula =$C_{11}H_{18}Ge$

3,5-Dimethylbromobenzene (0.410mL, 0.558g, 3.02mmol) was dissolved in anhydrous THF (15mL) under N_2 and cooled to -78°C. s-BuLi (1.3M, 3.5mL, 4.55mmol) was added slowly and dropwise and the resulting solution stirred for 5 minutes. Trimethylgermanium bromide (0.485mL, 0.749g, 3.79mmol) was then added dropwise and the reaction mixture stirred for 15 minutes. The CO_2/acetone bath was removed, and the reaction mixture stirred for a further 15 minutes before being quenched with distilled water (2mL) and partitioned between Et_2O (2 × 20mL) and H_2O (20mL). The organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. GC/MS of the crude reaction mixture indicated the presence of a significant amount of unreacted aryl bromide. The crude mixture was dissolved in THF (14mL) and exposed to n-BuLi (1.0mL, 2.5M, 2.5mmol) at -78°C for 30 minutes, before being quenched for a second time with trimethylgermanium bromide (0.490mL, 0.757g, 3.83mmol) and stirred for a further 15 minutes. Work up as before gave a crude mixture, which was purified by column chromatography (4 × 2cm Silica gel, eluting with petrol) to give xylylgermane **105** as a clear colourless liquid (0.464g, 2.08mmol, 69%). **R*f*** 0.74 (petrol); **^{1}H NMR** ($CDCl_3$) δ 0.52 (9H, s, $(CH_3)_3Ge$), 2.46 (6H, s, CH_3C), 7.11 (1H, s, $CH_3CCHCCH_3$), 7.24 (2H, s, $CH_3CCHC(Ge(CH_3)_3)CHCCH_3$); **^{13}C NMR** ($CDCl_3$) δ -1.7 (q), 21.5 (q), 130.1 (d), 130.7 (d), 137.3 (s), 142.4 (s); **IR** (neat) 2972, 2909, 1597, 1236, 1137, 828, 600 cm^{-1}; **MS** (EI) *m/z* 224 (M^{+} 11%), 209 (100%), 179 (11%), 119 (8%), 105 (16%); **HRMS** calc'd for $C_{11}H_{18}{}^{74}Ge$ 224.0620, found 224.0623, error –1.2ppm.

Trimethyl-(2,6-dimethylphenyl)-germane (107)

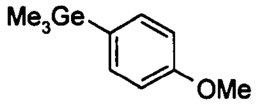


107

Molecular Weight =222.86
Molecular Formula =$C_{11}H_{18}Ge$

2,6-Dimethylbromobenzene (0.400mL, 0.556g, 3.00mmol) was dissolved in anhydrous THF (10mL) under N_2 and cooled to -78°C. n-BuLi (2.5M, 1.8mL, 4.50mmol) was added slowly and dropwise and the resulting solution stirred for 45 minutes. Trimethylgermanium bromide (0.490mL, 0.757g, 3.83mmol) was then added dropwise and the reaction mixture stirred for 45 minutes. The CO_2/acetone bath was removed, and the reaction mixture stirred for a further 30 minutes before being quenched with distilled water (2mL) and partitioned between Et_2O (2 × 20mL) and H_2O (20mL). The organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The resulting mixture was purified by column chromatography (4 × 2cm Silica gel, eluting with petrol) to give xylylgermane **107** as a clear colourless liquid (0.537g, 2.41mmol, 80%). **R*f*** 0.71 (petrol); **^{1}H NMR** ($CDCl_3$) δ 0.57 (9H, s, $(CH_3)_3Ge$), 2.48 (6H, s, CH_3C), 7.01-7.04 (2H, m, $CH_3CCHCHCHCCH_3$), 7.14-7.20 (1H, m, $CHCHCH$); **^{13}C NMR** ($CDCl_3$) δ 3.6 (q), 24.6 (q), 127.8 (d), 128.4 (d), 143.5 (s), one quaternary carbon not observed; **IR** (neat) 3052, 2968, 2909, 1566, 1448, 1236, 833, 768 cm^{-1}; **MS** (EI) *m/z* 224 (M^{+} 14%), 209 (100%), 179 (7%), 119 (20%), 105 (39%); **HRMS** calc'd for $C_{11}H_{18}{}^{74}Ge$ 224.0620, found 224.0622, error –0.6ppm.

Trimethyl-(4-methoxyphenyl)-germane (101)[221]

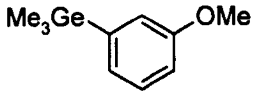


101

Molecular Weight =224.83
Molecular Formula =$C_{10}H_{16}GeO$

4-Bromoanisole (0.380mL, 0.568g, 3.04mmol) was dissolved in anhydrous THF (15mL) under N_2 and cooled to -78°C. s-BuLi (1.3M, 3.5mL, 4.55mmol) was added slowly and dropwise and the resulting solution stirred for 5 minutes. Trimethylgermanium bromide (0.485mL, 0.749g, 3.79mmol) was then added dropwise and the reaction mixture stirred for 15 minutes. The CO_2/acetone bath was removed, and the reaction mixture stirred for a further 15 minutes before being quenched with distilled water (2mL) and partitioned between Et_2O (2 × 20mL) and H_2O (20mL). The organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The resulting mixture was purified by column chromatography (4 × 2cm Silica gel, eluting with petrol/EtOAc, 9/1) to give *p*-anisylgermane **101** as a clear colourless liquid (0.605g, 2.69mmol, 89%). **R$_f$** 0.90 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 0.39 (9H, s, (C*H*$_3$)$_3$Ge), 3.83 (3H, s, OC*H*$_3$), 6.94 (2H, d, *J* 8.5, CH$_3$OCC*H*), 7.42 (2H, d, *J* 8.5, (CH$_3$)$_3$GeCC*H*); **MS** *m/z* (EI) 226 (M^{+} 6%), 211 (100%), 181 (17%), 121 (19%), 105 (13%), 89 (17%).

Trimethyl-(3-methoxyphenyl)-germane (102)[239]



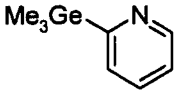
102

Molecular Weight =224.83
Molecular Formula =$C_{10}H_{16}GeO$

3-Bromoanisole (0.250mL, 0.369g, 1.97mmol) was dissolved in anhydrous THF (10mL) under N_2 and cooled to -78°C. s-BuLi (1.3M, 2.35mL, 3.06mmol) was added slowly and dropwise and the resulting solution stirred for 30 minutes. Trimethylgermanium bromide (0.310mL, 0.479g, 2.42mmol) was then added dropwise and the reaction mixture stirred for 30 minutes. The CO_2/acetone bath was removed, and the reaction mixture stirred for a further 30 minutes before being quenched with distilled water (2mL) and partitioned between Et_2O (2 × 15mL) and

H_2O (10mL). The organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The resulting mixture was purified by column chromatography (4 × 5cm Silica gel, eluting with petrol/EtOAc, 19/1) to give *m*-anisylgermane **102** as a clear colourless liquid (0.0867g, 0.386mmol, 20%). **R*f*** 0.39 (petrol); **^{1}H NMR** ($CDCl_3$) δ 0.39 (9H, s, $(CH_3)_3Ge$), 3.83 (3H, s, OCH_3), 6.86-6.90 (1H, m, GeCCHCHC*H*COCH$_3$), 7.03-7.09 (2H, m, Ar CH's), 7.31-7.34 (1H, m, GeCCHC*H*CHCOCH$_3$); **MS** *m/z* (EI) 226 (M^+ 11%), 211 (100%), 181 (13%), 105 (18%), 91 (19%).

Trimethyl-(2-pyridyl)-germane (108)[240,241]

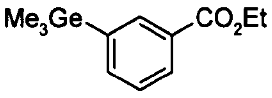


108

Molecular Weight =195.79
Molecular Formula =$C_8H_{13}GeN$

2-Bromopyridine (0.285mL, 0.472g, 2.99mmol) was dissolved in anhydrous THF (30mL) under N_2 and cooled to -78°C. n-BuLi (2.5M, 1.4mL, 3.50mmol) was added slowly and dropwise and the resulting solution stirred for 45 minutes. Trimethylgermanium bromide (0.450mL, 0.696g, 3.52mmol) was then added dropwise and the reaction mixture stirred for 30 minutes. The CO_2/acetone bath was removed, and the reaction mixture stirred for a further 30 minutes before being quenched with distilled water (2mL) and partitioned between Et_2O (2 × 20mL) and H_2O (20mL). The organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The resulting mixture was purified by column chromatography (4 × 2cm Silica gel, eluting with petrol/EtOAc, 8/2) to give pyridylgermane **108** as a clear colourless liquid (0.475g, 2.43mmol, 81%). **R*f*** 0.69 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 0.42 (9H, s, $(CH_3)_3Ge$), 7.11-7.17 (1H, m, Ar CH), 7.42-7.45 (1H, m, Ar CH), 7.50-7.54 (1H, m, Ar CH), 8.71-8.73 (1H, m, Ar CH); **MS** *m/z* (EI) 197 (M^+ 28%), 196 (37%), 182 (100%), 152 (94%), 93 (70%), 89 (50%).

Ethyl 3-(trimethylgermanyl)benzoate (110)



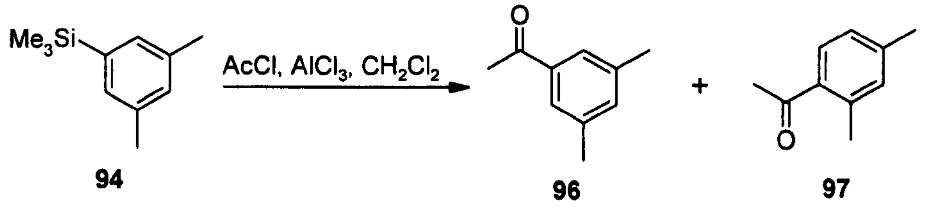
110

Molecular Weight =266.87
Molecular Formula =$C_{12}H_{18}GeO_2$

Ethyl 3-iodo-benzoate (0.490mL, 0.809g, 2.93mmol) was dissolved in anhydrous THF (30mL) under N_2 and cooled to -40°C. *iso*-Propyl magnesium chloride (2.0M in THF, 1.65mL, 3.3mmol) was then added slowly and dropwise, and the resulting mixture stirred for 90 minutes. Trimethylgermanium bromide (0.445mL, 0.687g, 3.48mmol) was then added slowly and dropwise and the reaction solution stirred for a further 2.75 hours before being quenched with aqueous NH_4Cl solution (1mL) and partitioned between CH_2Cl_2 (3 × 20mL) and distilled water (30mL). The organic extracts were dried with $MgSO_4$, filtered, then filtered through Silica gel and concentrated *in vacuo* to give *m*-benzoate **110** as a clear colourless liquid (0.581g, 2.18mmol, 74%). **R*f*** 0.79 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 0.46 (9H, s, $(CH_3)_3Ge$), 1.44 (3H, t, *J* 7.0, CH_2CH_3), 4.43 (2H, q, *J* 7.0, CH_2CH_3), 7.42-7.48 (1H, m, GeCCHC*H*CHCCO$_2$Et), 7.67-7.71 (1H, m, GeCC*H*CHCHCCO$_2$Et), 8.02-8.07 (1H, m, GeCCHCHC*H*CCO$_2$Et), 8.21 (1H, m, GeCC*H*CCO$_2$Et); **^{13}C NMR** ($CDCl_3$) δ -1.8 (q), 14.4 (q), 60.8 (t), 127.8 (d), 129.4 (d), 129.9 (s), 133.9 (d), 137.4 (d), 143.0 (s), 166.9 (s); **IR** (neat) 2977, 2908, 1715, 1590, 1367, 1261, 1117, 826, 742 cm^{-1}; **MS** *m/z* (EI) 268 (M^{+} 1%), 253 (100%), 225 (48%), 149 (17%), 119 (31%), 104 (28%), 91 (34%), 89 (32%); **HRMS** (ESI+) calc'd for $C_{12}H_{19}{}^{74}GeO_2$ 269.0597, found 269.0588, error –3.4ppm.

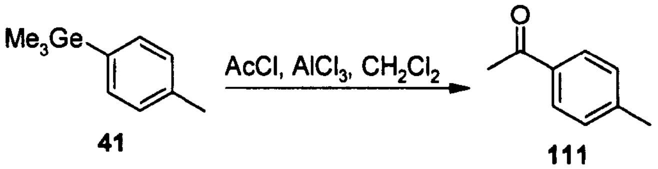
6.3.2 Acylation

General method for acylation: Acetylation of trimethyl-(3,5-dimethylphenyl)silane to give 3,5-dimethylacetophenone (96)[242] *and 2,4-dimethylacetophenone (97)*[243]



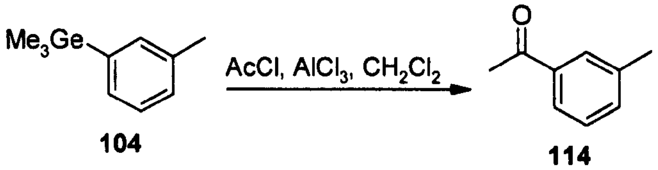
To a suspension of aluminium(III) chloride (0.0808g, 0.606mmol) in anhydrous CH_2Cl_2 (1mL) under nitrogen and cooled to 0°C with stirring, was added acetyl chloride (41μL, 0.0453g, 0.577mmol) dissolved in anhydrous CH_2Cl_2 (0.5mL) dropwise and slowly. The solution was then cooled further to -78°C. Silylxylene **94** (0.0859g, 0.502mmol) was dissolved in anhydrous CH_2Cl_2 (0.5mL) and added to the acetyl tetrachloroaluminate solution slowly and dropwise, before being stirred for 1 hour. The reaction was quenched with saturated aqueous NH_4Cl solution before being warmed to rt and extracted with CH_2Cl_2 (3 x 5mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product by column chromatography (4 x 6cm Silica gel, eluted with petrol/EtOAc, 9/1) gave an inseparable mixture of 3,5 and 2,4 dimethylacetophenones **96**[242] and **97**[243] respectively (0.0715g, 0.482mmol, 96%). **R_f** 0.42 (petrol/EtOAc, 9/1); **GC/MS R_t** 8.74min, **MS** *m/z* (EI) 148 ($M^{\cdot+}$ 44%), 133 (100%), 105 (61%), 77 (28%); **R_t** 9.11min, **MS** *m/z* (EI) 148 ($M^{\cdot+}$ 50%), 133 (100%), 105 (70%), 77 (28%).

Acetylation of trimethyl-(4-methyl-phenyl)-germane to give 4-methylacetophenone (111)[242]



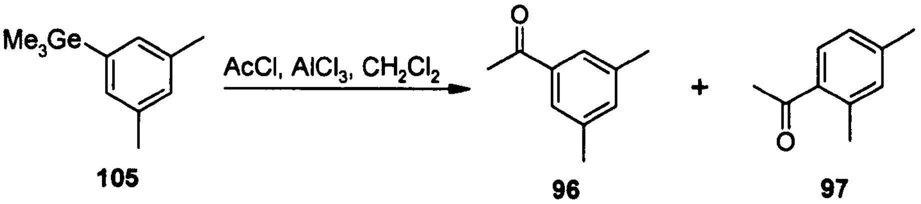
Using the general method above, but with aluminium(III) chloride (0.818g, 0.613mmol) in CH_2Cl_2 (1mL), acetyl chloride (41μL, 0.0453g, 0.577mmol) in CH_2Cl_2 (0.5mL) and *p*-tolylgermane **41** (0.0972g, 0.465mmol) in CH_2Cl_2 (0.5mL), to give 4-methylacetophenone **111** (0.0534g, 0.398mmol, 86%). **R*f*** 0.47 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 2.42 (3H, s, CH_3CO), 2.59 (3H, s, (CH_3C), 7.26 (2H, d, *J* 8.0, CH_3CCH), 7.87 (2H, d, *J* 8.0, CH_3COCCH); **MS** *m/z* (EI) 134 (M^+ 34%), 119 (100%), 91 (76%), 65 (26%).

Acetylation of trimethyl-(3-methylphenyl)-germane to give 3-methylacetophenone (114)[244]



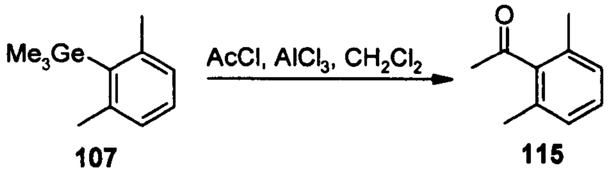
Using the general method above, but with aluminium(III) chloride (0.0803g, 0.602mmol) in CH_2Cl_2 (1mL), acetyl chloride (41μL, 0.0453g, 0.577mmol) in CH_2Cl_2 (0.5mL) and *m*-tolylgermane **104** (0.104g, 0.498mmol) in CH_2Cl_2 (0.5mL), to give 3-methylacetophenone **114** (0.0436g, 0.325mmol, 65%). **R*f*** 0.28 (petrol/EtOAc, 19/1); **^{1}H NMR** ($CDCl_3$) δ 2.42 (3H, s, CH_3CO), 2.61 (3H, s, CH_3C), 7.33-7.41 (2H, m, CH_3CCHCH), 7.75-7.79 (2H, m, $CHC(COCH_3)CH$); **MS** *m/z* (EI) 134 (M^+ 28%), 119 (100%), 91 (77%), 65 (28%).

Acetylation of trimethyl-(3,5-dimethyl-phenyl)-germane to give 3,5-dimethylacetophenone (96)[242] and 2,4-dimethylacetophenone (97)[243]



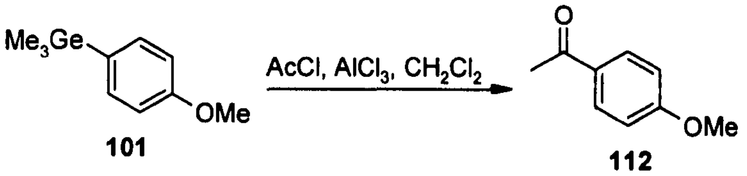
Using the general method above, but with aluminium(III) chloride (0.0798g, 0.598mmol) in CH_2Cl_2 (1mL), acetyl chloride (41μL, 0.0453g, 0.577mmol) in CH_2Cl_2 (0.5mL) and *m*-xylene **105** (0.112g, 0.503mmol) in CH_2Cl_2 (0.5mL), to give an inseparable mixture of isomers assigned as 3,5 and 2,4 dimethylacetophenones **96**[242] and **97**[243] (*cf.* Silylxylene **94**) 0.057g, 0.380mmol, 76%). **R*f*** 0.42 (petrol/EtOAc, 9/1); **GC/MS R*t*** 8.63min, **MS** *m/z* (EI) 148 (M^{+} 31%), 133 (100%), 105 (71%), 77 (25%); **R*t*** 8.98min, **MS** *m/z* (EI) 148 (M^{+} 34%), 133 (100%), 105 (86%), 77 (26%).

Acetylation of trimethyl-(2,6-dimethylphenyl)-germane to give 2,6-dimethylacetophenone (115)[244]



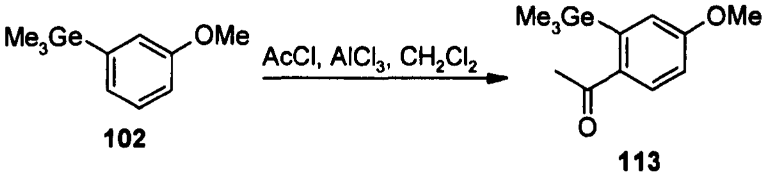
Using the general method above, but with aluminium(III) chloride (0.0807g, 0.605mmol) in CH_2Cl_2 (1mL), acetyl chloride (41μL, 0.0453g, 0.577mmol) in CH_2Cl_2 (0.5mL) and *o*-xylene **107** (0.112g, 0.503mmol) in CH_2Cl_2 (0.5mL), to give 2,6-dimethylacetophenone **115**. **R*f*** 0.31 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 2.26 (6H, s, C*H*$_3$C), 2.49 (3H, s, C*H*$_3$CO), 7.01-7.04 (2H, m, CH$_3$CC*H*), 7.14-7.20 (1H, m, CHC*H*CH); **MS** *m/z* (EI) 148 (M^{+} 24%), 133 (100%), 105 (81%), 77 (26%).

Acetylation of trimethyl-(4-methoxyphenyl)-germane to give 4-methoxyacetophenone (112)[242]



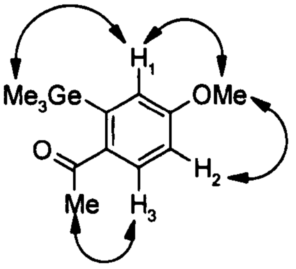
Using the general method above, but with aluminium(III) chloride (0.0833g, 0.624mmol) in CH_2Cl_2 (1mL), acetyl chloride (41μL, 0.0453g, 0.577mmol) in CH_2Cl_2 (0.5mL) and *p*-anisylgermane **101** (0.105g, 0.467mmol) in CH_2Cl_2 (0.5mL), to give 4-methoxyacetophenone **112** (0.0442g, 0.294mmol, 63%). **R*f*** 0.33 (petrol/EtOAc, 8/2); **^{1}H NMR** ($CDCl_3$) δ 2.56 (3H, s, COC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 6.93 (2H, d, *J* 9.0, CH_3OCC*H*), 7.94 (2H, d, *J* 9.0, CH_3COCC*H*); **MS** *m/z* (EI) 150 ($M^{\cdot+}$ 33%), 135 (100%), 107 (20%), 92 (25%), 77 (43%).

Acetylation of trimethyl-(3-methoxyphenyl)-germane to give 2-(trimethylgermyl)-4-methoxyacetophenone (113)



Using the general method above, but with aluminium(III) chloride (0.0837g, 0.628mmol) in CH_2Cl_2 (1mL), acetyl chloride (41μL, 0.0453g, 0.577mmol) in CH_2Cl_2 (0.5mL) and *m*-anisylgermane **102** (0.118g, 0.525mmol) in CH_2Cl_2 (0.5mL), to give acetylanisylgermane **113** (0.109g, 0.410mmol, 78%). **R*f*** 0.38 (petrol/EtOAc, 9/1); **^{1}H NMR** ($CDCl_3$) δ 0.41 (9H, s, Ge(C*H*$_3$)$_3$), 2.58 (3H, s, COC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 6.89 (1H, dd, *J* 8.5 and 3.0, CH_3OCC*H*CHCCOCH$_3$), 7.21 (1H, d, *J* 3.0, $(CH_3)_3$GeCC*H*), 7.91 (1H, d, *J* 8.5, CH_3COCC*H*); **IR** (neat) 2964, 1677, 1587, 1563, 1269, 1227, 1045, 827 cm^{-1}; **^{13}C NMR** ($CDCl_3$) δ 0.0 (q), 26.8 (q), 55.1 (q), 111.9 (d), 121.2 (d), 132.5 (d), 143.3 (s), 167.2 (s), two quaternary carbons not observed; **MS** *m/z* (EI) 253 ($[M\text{-}Me^{\cdot}]^+$ 100%), 238 (11%), 223 (27%), 119 (23%), 89 (18%); **HRMS** (EI) calc'd for $C_{12}H_{18}{}^{74}GeO_2$ 268.0519, found 268.0521, error –0.7ppm.

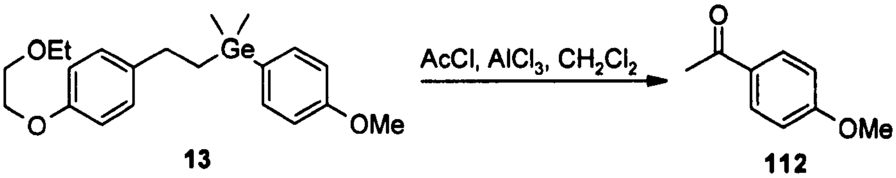
^{1}H NMR 1d *nOe* experiment:



H_1 δ 7.21ppm
H_2 δ 6.89ppm
H_3 δ 7.91ppm

Irradiation of the trimethylgermyl protons at δ 0.41ppm gave a response at δ 7.21ppm (H_1), irradiation of the methoxy protons at δ 3.88ppm gave responses at δ 7.21ppm (H_1) and δ 6.89ppm (H_2), whilst irradiation of the acyl protons at δ 2.58ppm gave a response at δ 7.91ppm (H_3), thus confirming the above substitution pattern.

Acetylation of anisylgermane 13 to give 4-methoxyacetophenone (112)[242]



Using the general method above, but with aluminium(III) chloride (0.0602g, 0.451mmol) in CH_2Cl_2 (1mL), acetyl chloride (35μL, 0.0387g, 0.493mmol) in CH_2Cl_2 (0.5mL) and anisylgermane **13** (0.140g, 0.347mmol) in CH_2Cl_2 (0.5mL), to give 4-methoxyacetophenone **112** (0.0273g, 0.182mmol, 52%). Analytical data as above.

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8 Appendices

8.1 Appendix 1: Solvents

All solvents were distilled prior to use. Petrol refers to the fraction of petroleum ether boiling between 40°C and 60°C. Cold solvents were pre-cooled to 0°C with ice. Commercial solvents for work-up and chromatography were distilled before use. Anhydrous solvents were either purchased or prepared as follows:[245]

CH_2Cl_2	Distilled from CaH_2 under nitrogen immediately prior to use.
1,4-Dioxane	Distilled from sodium/benzophenone under nitrogen immediately prior to use.
DMF	Refluxed with CaH_2 under nitrogen, distilled under reduced pressure and stored over 4Å molecular sieves under nitrogen.
Et_2O	Distilled from sodium/benzophenone under nitrogen immediately prior to use.
EtOH	Distilled from 4Å molecular sieves under nitrogen, and stored over 4Å molecular sieves under nitrogen.
$MeNO_2$	Distilled from CaH_2 under nitrogen immediately prior to use.
THF	Distilled from sodium/benzophenone under nitrogen immediately prior to use.
Toluene	Distilled from sodium under nitrogen immediately prior to use.

8.2 Appendix 2: Reagents

Chemicals were handled in accordance with COSHH regulations, and were used as commercially supplied with the following exceptions:

AcCl	Refluxed withPCl_5, then distilled from quinoline.[245]

BnTMAF	Commercially supplied in anhydrous form, stored over P_2O_5 under vacuum in a dessicator. Weighed out into sealed vials, under a stream of N_2 gas from an inverted funnel.
CsF	Commercially supplied in anhydrous form, stored over P_2O_5 under vacuum in a dessicator. Weighed out into sealed vials, under a stream of N_2 gas from an inverted funnel.
Et_3SiH	Distilled from CaH_2 under nitrogen and used immediately.

8.3 Appendix 3: GC/MS methods

The GC/MS system was a Perkin Elmer AutoSystem XL GC and autosampler, with Perkin Elmer Turbomass spectrometer, using the following conditions.

GC/MS method for sections 6.2.1 and 6.2.2

Ionisation Mode	EI (EI/CI combination source)
Column	BPX-5
Carrier Gas	Helium
Carrier gas flow rate	1mL/min
Injection Volume	1μL
Split ratio	24:1
Injection temperature	260°C
Temperature Gradient	160°C rising to 260°C at 5°C/min. Hold at 260°C for 10min.
Run Time	30 min

GC/MS method for sections 6.2.3, 6.2.4 and 6.2.5

Ionisation Mode	EI (EI/CI combination source)
Column	ZB-5 30m × 0.32mm × 0.25um FT
Carrier Gas	Helium
Carrier gas flow rate	1mL/min
Injection Volume	1μL
Split ratio	24:1
Injection Temperature	260°C
Temperature Gradient	60°C rising to 260°C at 10°C/min. Hold at 260°C for 10min.
Run Time	30 min

8.4 Appendix 4: LC/MS methods

The LC/MS system was an Agilent 1100 HPLC and a Fisons VG Platform mass spectrometer, using the following conditions.

Ionisation Mode	ESI +ve and ESI –ve	
Column	Supelcosil LC ABZ+PLUS (3.3cm × 4.6mm)	
Solvent A	0.1% v/v HCO_2H and 0.1 M NH_4OAc in water	
Solvent B	0.05% v/vHCO_2H and 5% v/v water in MeCN	
Gradient	**Time/min**	**Solvent B %**
	0	0
	0.7	0
	4.2	100
	5.3	0
	5.5	0
Flow rate	3mL/min	
Run Time	5.5min	