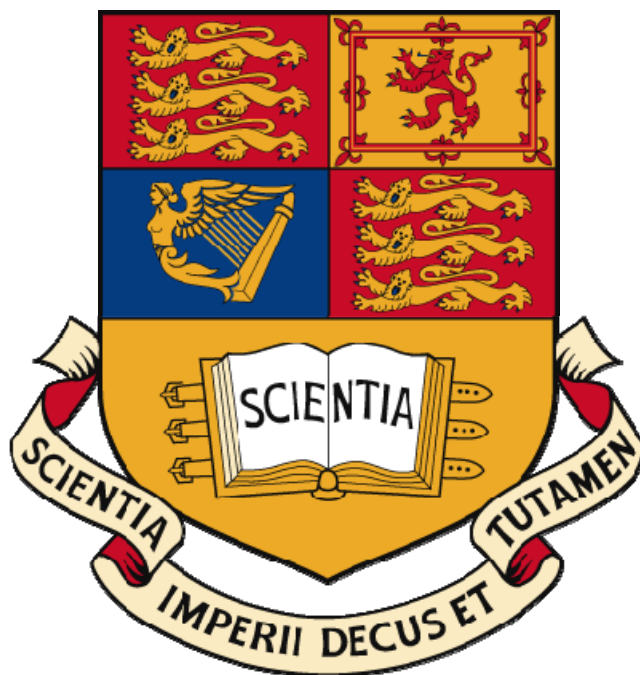


# **The Synthesis of Bioactive Compounds by Using Phase-tagged Germanium Chemistry**

Thesis submitted for the fulfilment of a PhD degree



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Imperial College London was the place where I pursued doctoral education and training. The College has not only provided sufficient resources for scientific research, but also an extraordinary environment for study. As the College's motto states: '*Scientia imperii decus et tutamen; Knowledge is the adornment and protection of the Empire*', knowledge is the most valuable treasure and possession, and has been my dogma throughout my doctoral studies.

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## Abbreviations

|                       |                                                               |
|-----------------------|---------------------------------------------------------------|
| Ac                    | Acetyl                                                        |
| aq                    | Aqueous                                                       |
| Alk                   | Alkyl                                                         |
| Ar                    | Aryl                                                          |
| ax                    | Axial                                                         |
| brs                   | Broad singlet                                                 |
| Bn                    | Benzyl                                                        |
| Bu or <sup>n</sup> Bu | Butyl                                                         |
| cat.                  | Catalytic amount                                              |
| CB1                   | Cannabinoid receptor 1                                        |
| <i>cf.</i>            | <i>confer</i> ; Latin: “compare”                              |
| CI                    | Chemical ionisation                                           |
| CNS                   | Central nervous system                                        |
| conc.                 | Concentrated                                                  |
| 3-CPBA                | 3-Chloroperbenzoic acid                                       |
| Cy                    | Cyclohexyl                                                    |
| d                     | Doublet                                                       |
| DBU                   | 1,8-Diazabicyclo[5.4.0]undec-7-ene                            |
| DCC                   | Dicyclohexylcarbodiimide                                      |
| DCT                   | Dichloroamine T                                               |
| Dde                   | <i>N</i> -[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl] |
| DMAP                  | 4-( <i>N,N</i> -Dimethylamino)pyridine                        |
| DMF                   | <i>N,N</i> -Dimethylformamide                                 |
| DOSY                  | Diffusion-ordered spectroscopy                                |
| dppp                  | 1,3-Bis(diphenylphosphino)propane                             |
| E                     | Electrophile                                                  |
| EC                    | Electron capture                                              |
| EE                    | Ethyl ethoxy                                                  |
| <i>e.g.</i>           | <i>exempli gratia</i> ; Latin: “for example”                  |
| EI                    | Electron impact                                               |
| eq.                   | Equivalents                                                   |

|                 |                                        |
|-----------------|----------------------------------------|
| eq              | Equatorial                             |
| ESI             | Electron spray ionisation              |
| Et              | Ethyl                                  |
| EtOH            | Ethanol                                |
| FAB             | Fast-atom bombardment                  |
| FC              | Flash chromatography                   |
| FC-72           | Perfluorohexane                        |
| F-LLE           | Fluorous liquid-liquid extraction      |
| Fmoc            | 9-Fluorenylmethoxycarbonyl             |
| F-SPE           | Fluorous solid-phase extraction        |
| $\gamma$        | Surface tension                        |
| GC/MS           | Gas chromatography-mass spectrometry   |
| h               | Hours                                  |
| HOAc            | Acetic acid                            |
| HOMO            | Highest occupied molecular orbital     |
| HPLC            | High performance liquid chromatography |
| HRMS            | High resolution mass spectrometry      |
| Hunig's base    | Diisopropylethylamine                  |
| h $\nu$         | Photons                                |
| <i>i</i>        | <i>Iso</i>                             |
| <i>i.e.</i>     | <i>id est</i> ; Latin: "that is"       |
| <i>in situ</i>  | Latin: "in the place"                  |
| <i>in vacuo</i> | Latin: "in a vacuum"                   |
| IR              | Infra-red                              |
| KOTMS           | Potassium trimethylsilonate            |
| LHMDS           | Lithium hexamethyldisilazide           |
| LL              | Loading level                          |
| LUMO            | Lowest unoccupied molecular orbital    |
| <i>m</i>        | <i>Meta</i>                            |
| m               | Multiplet                              |
| min             | Minutes                                |
| Me              | Methyl                                 |
| MeCN            | Acetonitrile                           |

|                                       |                                                                                                       |
|---------------------------------------|-------------------------------------------------------------------------------------------------------|
| MeOH                                  | Methanol                                                                                              |
| mp                                    | Melting point                                                                                         |
| MS                                    | Mass spectrometry                                                                                     |
| NCS                                   | <i>N</i> -Chlorosuccinimide                                                                           |
| NIS                                   | <i>N</i> -Iodosuccinimide                                                                             |
| NMP                                   | <i>N</i> -Methyl-2-pyrrolidone                                                                        |
| NMR                                   | Nuclear magnetic resonance                                                                            |
| Np                                    | Naphthalenyl                                                                                          |
| Nu                                    | Nucleophile                                                                                           |
| <i>o</i>                              | <i>Ortho</i>                                                                                          |
| OAc                                   | Acetoxy                                                                                               |
| OTf                                   | Trifluoromethanesulfonate (triflate)                                                                  |
| Oxone <sup>®</sup>                    | Triple salt with the formula of 2KHSO <sub>5</sub> -KHSO <sub>4</sub> -K <sub>2</sub> SO <sub>4</sub> |
| <i>p</i>                              | <i>para</i>                                                                                           |
| Petro                                 | Petroleum spirits (bp. 40~60 °C)                                                                      |
| Ph                                    | Phenyl                                                                                                |
| Pd(PPh <sub>3</sub> ) <sub>4</sub>    | Tetrakis(triphenylphosphine)palladium                                                                 |
| PdCl <sub>2</sub> (MeCN) <sub>2</sub> | Bis(acetonitrile)dichloropalladium                                                                    |
| Pr                                    | Propyl                                                                                                |
| q                                     | Quartet                                                                                               |
| quint                                 | Quintet                                                                                               |
| PET                                   | Positron emission tomography                                                                          |
| PS                                    | Polystyrene                                                                                           |
| R <sub>f</sub>                        | Perfluoroalkyl                                                                                        |
| RT                                    | Room temperature                                                                                      |
| s                                     | Singlet                                                                                               |
| SAR                                   | Structure-activity relationship                                                                       |
| sat.                                  | Saturated                                                                                             |
| SET                                   | Single electron transfer                                                                              |
| Selectfluor <sup>®</sup>              | 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo-<br>[2.2.2]octane bis(tetrafluoroborate)                  |
| SPECT                                 | Single photon emission computed tomography                                                            |
| SPOS                                  | Solid-phase organic synthesis                                                                         |

|                                                                                   |                                              |
|-----------------------------------------------------------------------------------|----------------------------------------------|
| <i>t</i> or <i>tert</i>                                                           | Tertiary                                     |
| t                                                                                 | Triplet                                      |
| $\tau$                                                                            | Torsional angle                              |
| TBAF                                                                              | Tetra- <i>n</i> -butylammonium fluoride      |
| TBAI                                                                              | Tetra- <i>n</i> -butylammonium iodide        |
| TFA                                                                               | Trifluoroacetic acid                         |
| THF                                                                               | Tetrahydrofuran                              |
| TLC                                                                               | Thin-layer chromatography                    |
| TMDS                                                                              | Tetramethyldisiloxane                        |
| TMH                                                                               | Transmembrane helical                        |
| TMEDA                                                                             | <i>N,N',N,N'</i> -tetramethylethylenediamine |
| TMG                                                                               | Trimethylgermyl                              |
| TMS                                                                               | Trimethylsilyl                               |
|  | Solid-phase support                          |
| Tol                                                                               | Tolyl                                        |
| UV                                                                                | Ultraviolet                                  |
| UQ                                                                                | Ubiquinone                                   |
| UQH <sub>2</sub>                                                                  | Ubiquinol                                    |
| <i>vide infra</i>                                                                 | Latin: “see below”                           |

# Abstract

The research described in this thesis covers two fields of investigation:

## **1) Biaryl and styrene Synthesis by Cross-Coupling of Fluorous-tagged Photo-activated Arylgermanes and Towards the Preparation of Boscalid and Analogues**

Biaryls are generally prepared by cross-coupling between aryl metals. However, even the most robust of these aryl metal species cannot be carried through complex synthetic sequences due to their reactivity particularly towards electrophiles. In this thesis, the development of trialkylgermanes as ‘safety-catch’ coupling precursors for biaryl and styrene synthesis was achieved. The safety-catch germanes are fluorous-tagged to facilitate parallel synthesis using fluorous SPE techniques and are activated towards Pd(0)-catalysed cross-coupling with aryl bromides by oxidative photolysis using a UV lamp. The stability profile of the fluorous-tagged arylgermanes was examined. They are stable under strong basic, nucleophilic and reductive conditions but labile in acidic and oxidative environments. This stability profile provides unique opportunities for synthetic route design in target orientated syntheses by allowing the germane group to be installed early in the sequence but only activated for cross-coupling when required. This method has been applied to the synthesis of the plant anti-fungal agent boscalid<sup>®</sup> and its alkynyl derivatives.

## **2) Novel Protocol for Solid Phase Synthesis of Radio-iodinated Ligands for Imaging of Cannabinoid Receptors in the Brain**

Rimonabant<sup>®</sup> is a CB1 receptor antagonist indicated for the treatment of obesity, metabolic syndrome, addiction and smoking cessation. Radio-labelled analogues are potential PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography) imaging agents for visualising the distribution of cannabinoid receptors in the brain for medical research. Conventional methods for the preparation of radio-iodinated cannabinoid receptor ligands employ organostannane precursors which undergo electrophilic *ipso*-iododestannylation with concomitant formation of toxic organostannane by-products. Rigorous removed of organostannane residues is necessary prior to injection the ligand for *in vivo* experiments. In this thesis, a novel, non-toxic, solid-supported and facile approach for the parallel synthesis of iodinated cannabinoid receptor ligands based on the skeleton of rimonabant has been demonstrated.

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## 1. Introduction

The research described in this thesis is focused on the development of phase-tagged organogermanes to achieve: (i) ‘safety-catch’ germyl-Stille cross coupling with aryl bromides to furnish biphenyls and styrenes and (ii) parallel synthesis of iodobisarylpyrazole-based cannabinoid receptor (CB1) inverse agonists *via ipso-iododegermylation*.

Phase-tagged arylgermanes have been demonstrated to be robust and facile coupling partners that can withstand a wide range of chemical manipulation procedures as exemplified by a novel synthesis of the anti-fungal agent boscalid<sup>®</sup> and its derivatives. In addition, alkenyl germanes have been shown to be competent partners for cross coupling with aryl bromides to give styrenes.

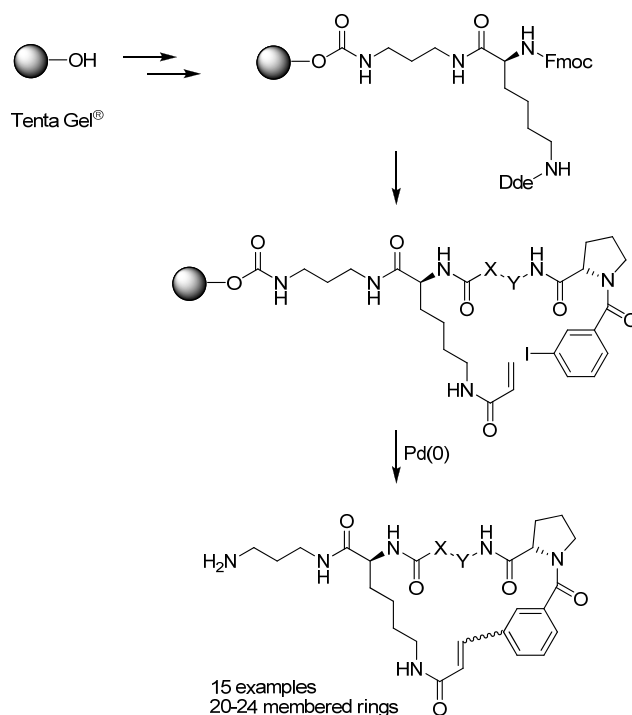
The iododegermylation method was developed to provide ‘proof-of-concept’ for liberation of radio-active CB1 inverse agonists for positron emission tomography (PET) and single photon emission computed tomography (SPECT).

The following sections of this introduction provide pertinent background information to several key areas of chemistry that relate directly to the above work as presented later in this thesis.

### 1.1 Solid-Phase Methods in Organic Synthesis

Since the first introduction of solid-phase peptide and oligosaccharide synthesis by Merrifield in 1963,<sup>1</sup> solid-phase organic synthesis (SPOS) has been widely adopted by organic chemists to achieve combinatorial synthesis of structurally diverse pharmaceutical molecular libraries. The key concept for SPOS methodology is to tether a simple molecule onto an insoluble polymer-support and then build-up complexity by planned chemical transformations and then cleave the final product off the resin (Merrifield’s protocol). There are several advantages of SPOS over normal solution phase approaches. One major benefit is the facile separation and purification of intermediates by simple filtration of the reaction mixture. Moreover, due to this ease of purification, all transformations applied during SPOS can be achieved using a large excess of reagents to drive reactions to completion. In addition,

a so-called 'pseudo-dilution effect'<sup>2</sup> is pronounced and facilitates macrocyclisation in SPOS relative to in solution phase synthesis. For example in 1995, Hauske introduced an acid-labile carbamate linker to deliver, high purity products following macrocyclisation of 'drug-like' libraries mediated by Pd(0) under mild conditions. All of the macrocycles (20- to 24-membered rings) were liberated from the resins under traceless cleavage conditions and obtained in good overall yields (Scheme 1.1.1).<sup>3</sup>



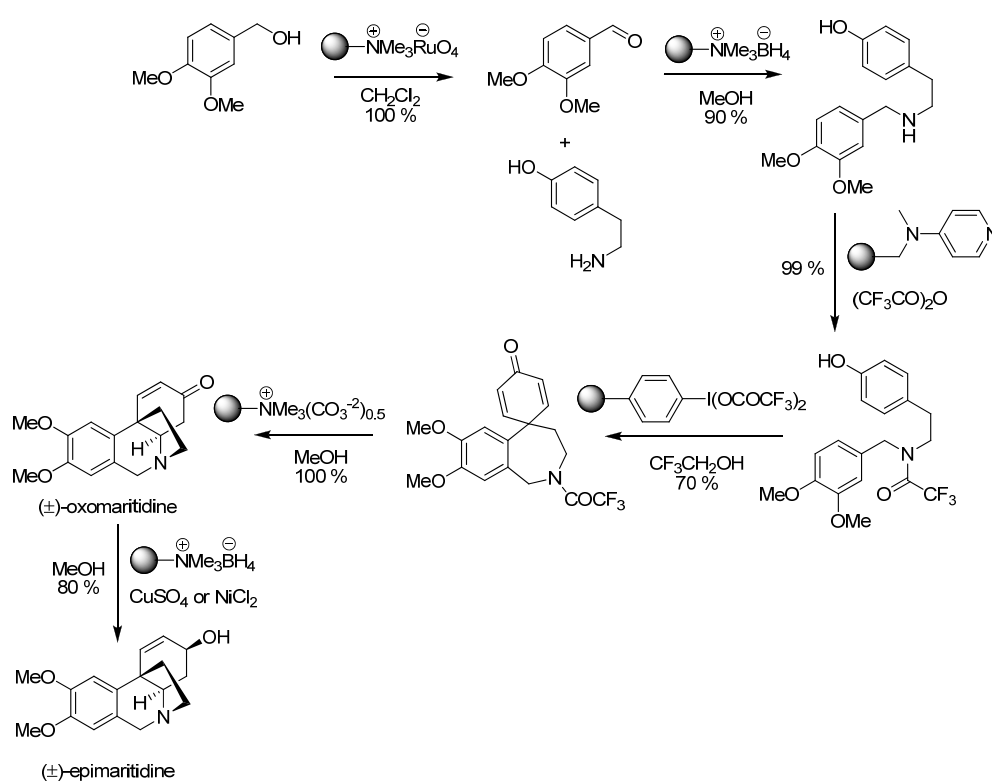
**Scheme 1.1.1** Hauske's macrocyclisation on a solid-support resins.<sup>3</sup>

Although Merrifield's protocol for SPOS has many advantages over conventional solution phase reactions, it has some drawbacks: functionalised resins are difficult to characterise and reactions are difficult to monitor in real time in comparison with solution phase chemistry; reaction rates can be slow; extra steps are necessary to anchor and to release substrates from the resin; convergent synthetic strategies are not applicable; and certain reactions can only be carried out on specific types of resin.

Some of these disadvantages can be overcome by introducing solid-supported reagents which are reactive chemicals immobilised on a polymer-support resin for carrying out chemical transformations in solution (Ley's protocol).<sup>4</sup> This concept also encompasses the development of solid-supported scavengers to remove excess organic or metallic reagents from solution phase reactions. Solid-supported reagents

and scavengers facilitate *in situ* purification of reaction mixtures, leaving the desired products in solution for convenient identification. Conventional multi-step transformations in solution can be performed using sequential solid-supported reagents and scavengers to telescope workup and purification procedures. In addition, this approach can also be applied to convergent syntheses to achieve higher reaction yields than in the corresponding linear counterparts.

Ley demonstrated the former facet by employing solid-supported reagents to effect the clean and efficient total synthesis of several natural products (*e.g.* oxomartidine and epimartidine) (Scheme 1.1.2).<sup>5</sup>



**Scheme 1.1.2** Ley's total synthesis of (±)-oxomartidine and (±)-epimartidine.<sup>5</sup>

Both the Merrifield and the Ley approaches to SPOS have been widely applied in automated combinatorial and parallel synthesis in industry for rapidly preparing drug-like small molecules for property screening (*e.g.* as new pharmaceuticals). However, slower conversion rates than for the corresponding transformations in solution remains a weakness due to the biphasic interactions between the polymer and solution.

## 1.2 Fluorous-Phase Technology in Organic Synthesis

To circumvent the drawbacks inherent to solid-supported technologies, alternative approaches using homogeneous 'beadless' phase-tagged chemistry have been introduced to facilitate separation whilst retaining solution phase kinetics. Among all of these beadless approaches, fluorous phase-tag anchoring of substrates to enable easy separation, monitoring, analysis and characterisation has become the method of choice. Fluorous-phase synthesis was pioneered by Zhu<sup>6</sup> followed by extensive studies in this field by Horváth and Rabái,<sup>7</sup> and by Curran.<sup>8</sup>

The unique chemical interactions between perfluoroalkyl chains and fluorous-rich environments is the essential element in fluorous synthesis. Perfluoroalkyl chains  $[\text{CF}_3(\text{CF}_2)_m(\text{CH}_2)_n]$  which will be abbreviated as  $R_f$  in this thesis] consist of two parts: the perfluoroalkyl and the alkyl domains. The perfluoroalkyl part dominates the affinity of the whole molecule with a fluorous phase to effect easy separation; the alkyl part isolates the electron deficient perfluoroalkyl domain from reaction sites of anchored substrates. Generally,  $R_f$ -tags are chemically inert to reaction conditions. The term 'heavy fluorous' is applied to molecules bearing more than 60 % fluorine by weight, whereas 'light fluorous' indicates those with less than 40 % of fluorine by weight.

### 1.2.1 Application of heavy fluorous-tags in organic synthesis

Heavy fluorous compounds display high affinity for fluorous solvents and form biphasic layers with organic solvents at certain temperature ranges. At elevated reaction temperatures, monophasic behaviour is observed and reactions proceed as in conventional solution phase conditions. Upon cooling down, biphasic behaviour is observed and the organic and fluorous compounds are partitioned into the two layers, allowing them to be separated (Figure 1.2.1).<sup>7,9</sup>

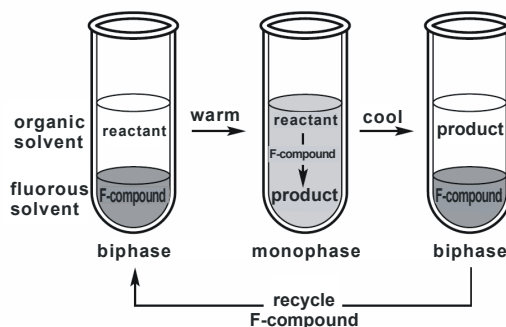


**Figure 1.2.1** Fluorous biphasic reaction system for *in situ* separation of organic product from fluororous compounds.<sup>7,9</sup>

Fluorous solvents are of higher density than organic solvents and water, and specifically solvate  $R_f$ -tagged compounds. This property is employed for fluororous liquid-liquid extractions (F-LLE). Heavy fluororous compounds can be separated from organic and water-soluble components by a triphasic liquid-liquid extraction procedure (Figure 1.2.2).<sup>10</sup>

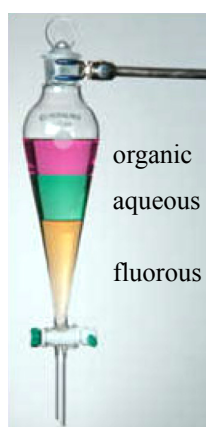
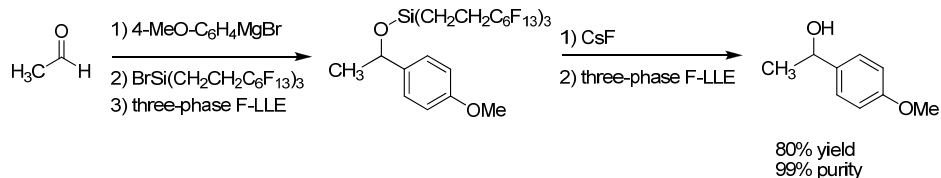


**Figure 1.2.2** Three-phase fluororous liquid-liquid extraction (F-LLE).<sup>10</sup>

Curran reported a triphasic fluororous liquid-liquid extraction procedure to demonstrate how a  $R_f$ -tag could be attached and then released from a substrate to facilitate purification of intermediates during addition of a Grignard reagent to an aldehyde.<sup>8</sup> The  $R_f$ -tagged intermediate was retained in the fluororous layer (FC-72) of the three phase extraction, whereas the  $R_f$ -tag-free desired product was released into the organic layer in high yield and purity (Scheme 1.2.1).



**Scheme 1.2.1** Curran's three-phase F-LLE concept to effect a simple separation.<sup>8</sup>

However, to achieve high partition coefficients of *R<sub>f</sub>*-tagged components in F-LLE, a large number of fluorine atoms (60 or more) are required. Consequently, these heavy *R<sub>f</sub>*-tagged molecules are not atom economic for synthesis.

### 1.2.2 Recent developments in light fluorous-tagged chemistry

In order to meet the criteria for the development of atom economic and automated phase-tagged methodology, light *R<sub>f</sub>*-tags were introduced. Due to the low affinity of light *R<sub>f</sub>*-tagged compounds for fluorous solvents, they are not efficiently separated by triphasic fluorous liquid-liquid extraction. Curran therefore addressed the separation of light *R<sub>f</sub>*-tagged molecules by introducing fluorous solid-phase extraction (F-SPE)<sup>11</sup> and reverse phase fluorous HPLC (RP F-HPLC).<sup>12</sup> These technologies constitute more reliable and rapid technologies than F-LLE, and have been automated in industry for high-throughput organic synthesis and combinatorial chemistry.<sup>13-15</sup>

Light *R<sub>f</sub>*-tagged compounds generally have similar physical properties to their tag-free congeners (*e.g.* polarity, reactivity and solubility) and can be envisaged to give a comparable outcome when applying literature conditions reported in solution phase without serious modification. Moreover, reactions, intermediates and products with a light *R<sub>f</sub>*-tag can be monitored and characterised by TLC, IR, NMR and MS, and can be easily separated from non *R<sub>f</sub>*-tagged compounds by F-SPE.

The stationary phase of an F-SPE cartridge is a *R<sub>f</sub>*-chain grafted reverse phase silica gel. FluoroFlash<sup>®</sup> are commercial and the F-SPE cartridges are available in various loading capacity with *R<sub>f</sub>* length of C<sub>8</sub>F<sub>17</sub>. This method relies on strong interactions between the *R<sub>f</sub>*-chains on the stationary phase and on the *R<sub>f</sub>*-tagged compounds.

Perfluoroorganic compounds have strong affinity to fluorous solvents and fluorous reverse-phase silica gel. This is probably resulting from the extremely low surface

tension ( $\gamma$ ) of perfluoroorganic compounds in comparison with ordinary organic solvents (*e.g.*  $\gamma_{\text{MeCN}} = 28.5$ ;  $\gamma_{\text{THF}} = 26.9$ ;  $\gamma_{\text{MeOH}} = 22.4$  at 25 °C) and water ( $\gamma_{\text{water}} = 72$ ). The low surface tension of perfluoroalkanes have the tendency to aggregate forming films by excluding solvent from between the perfluoro chains on the *Rf*-tagged compounds and those on the fluororous stationary phase of the F-SPE cartridge. This is prevalent under the solvent system with high surface tension (fluorophobic solvents). As such, this promotes the van der Waals forces of the perfluoroalkyl functionalities, resulting in high affinity of the two fluororous components.<sup>16</sup>

Upon loading a mixture of *Rf*-tagged and non-fluorous components onto a pre-conditioned F-SPE cartridge, the non-fluorous compound can be washed off with fluorophobic solvents (typically 50:50  $\rightarrow$  80:20 MeOH-H<sub>2</sub>O,  $\gamma_{\text{MeOH(aq)}} = 35.5$  and 27.4, respectively).<sup>17</sup> By decreasing the percentage of water, the surface tension of the mobile phase is reduced and that alters the behaviour of this system into fluorophilic solvents (*e.g.* 100% MeOH, MeCN or THF). Fluorophilic solvents are pervasive between perfluoroalkanes hence breaking the interaction amongst them. Therefore, the *Rf*-tagged compound is then eluted by these solvents.

An example using the F-SPE procedure to separate an *Rf*-tagged orange dye from a non-fluorous blue dye is shown below (Figure 1.2.3).<sup>10</sup>

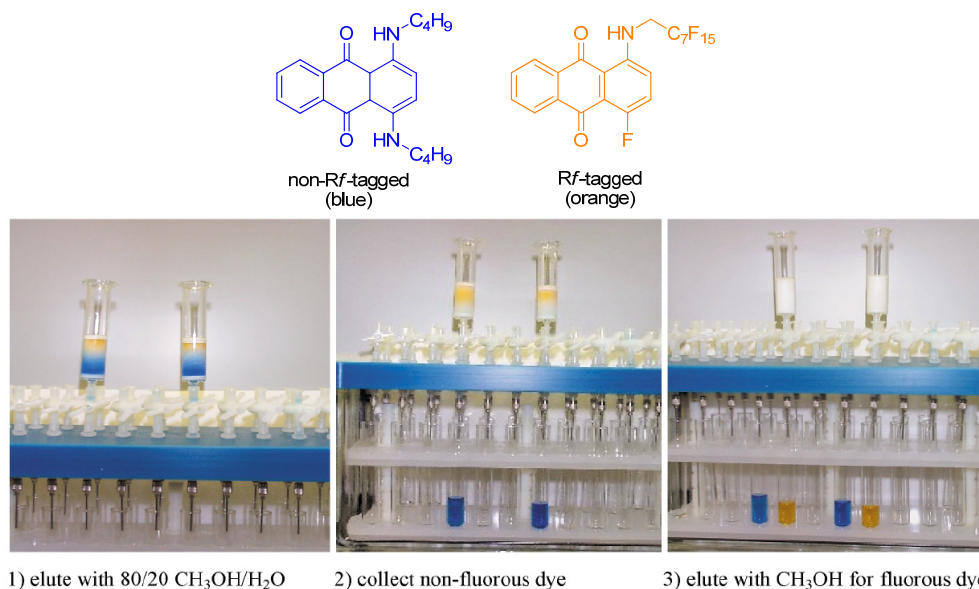
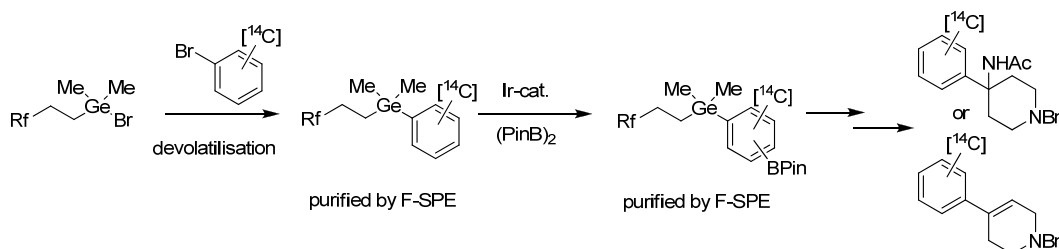


**Figure 1.2.3** An F-SPE demonstration of the separation of a *Rf*-tagged dye (orange) and non-fluorous dye (blue).<sup>10</sup>

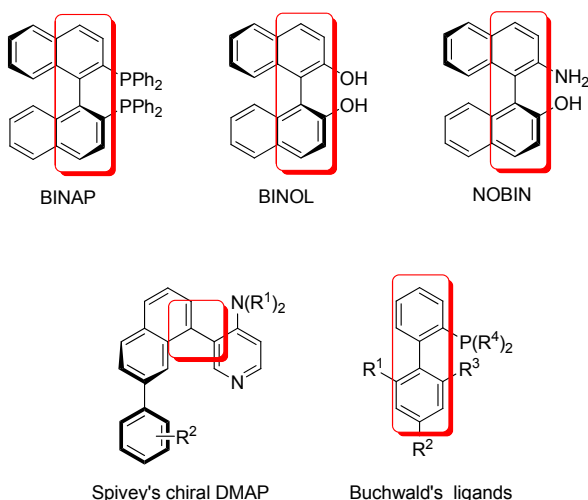
Our group has reported a proof-of-concept study for isotope containment during the preparation of potentially  $^{14}\text{C}$  labelled 4-phenylpiperidine pharmacophores by use of a light Rf-tagged germanium linker to devolatilise labelled-bromobenzene and allow use of the F-SPE method to purify all intermediates (Scheme 1.2.2).<sup>18</sup>



**Scheme 1.2.2** Spivey's proof-of concept study using a light Rf-tagged germanium linker to achieve devolatilisation of potentially  $^{14}\text{C}$ -labelled bromobenzene and rapid purification during synthesis of pharmacophores.<sup>18</sup>

### 1.3 Biaryls - Importance and Synthesis

Biaryls are pervasive structural motifs in natural products,<sup>19</sup> agrochemicals,<sup>20</sup> and dyes. Polyaromatics are key structures in dye-sensitized solar cells (DSSCs)<sup>21</sup> and organic light-emitting devices (OLEDs).<sup>22</sup> Biaryl scaffolds introduced in drug-like small molecules have been used to increase inhibitor-receptor binding affinities<sup>23</sup> and for inhibition of protein-protein interactions<sup>24</sup> during the development of new drugs. Statistical data reveals that greater than 4.3% of all pharmaceuticals bear this subunit.<sup>23</sup> In addition, biaryls are found in many organocatalysts (*e.g.* Spivey's chiral DMAP)<sup>25</sup> and ligands (*e.g.* Noyori's BINAP,<sup>26</sup> BINOL<sup>27</sup> and Kocovsky's NOBIN<sup>28</sup>) for asymmetric synthesis. Recently, a family of dialkylbiaryl phosphine ligands have been developed by Buchwald<sup>29</sup> that form highly reactive complexes with transition metals such as Pd(0) for applications in catalytic chemistry (Scheme 1.3.1).



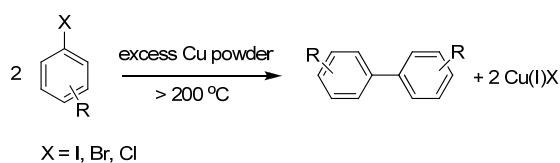
**Scheme 1.3.1** Examples of organocatalysts and ligands containing biaryl units.

The below section briefly reviews methods to the construction of aryl-aryl bonds including *via* copper mediated coupling reactions, nucleophilic substitution and aryne intermediates. More recent approaches involving palladium catalysed cross-coupling of aryl halides with organostannanes (Stille coupling), organosilanes (Hiyama-Denmark coupling) and organogermanes (germyl-Stille coupling) will be discussed in Chapter 2 of this thesis.

### 1.3.1 Copper mediated biaryl bond formation

#### 1.3.1.1 The Ullmann Reaction

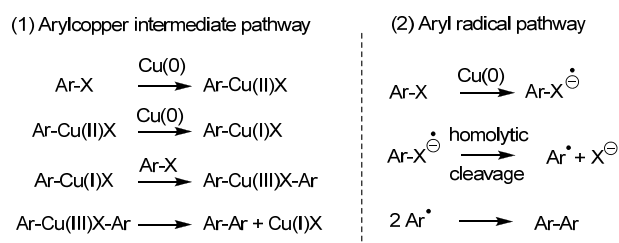
The formation of aryl-aryl bonds is a crucial transformation in synthetic chemistry. The first research into biaryl bond formation research was reported by Ullmann in 1901<sup>30</sup> and since then, hundreds of methods of biaryl coupling have been reported. Ullmann reported subjecting aryl halides with an excess amount of copper powder at elevated temperature (over 200 °C) to give a symmetrical biaryl and a copper halide (Scheme 1.3.2).<sup>30</sup>



**Scheme 1.3.2** Ullmann's biaryl formation using Copper powder.<sup>30</sup>

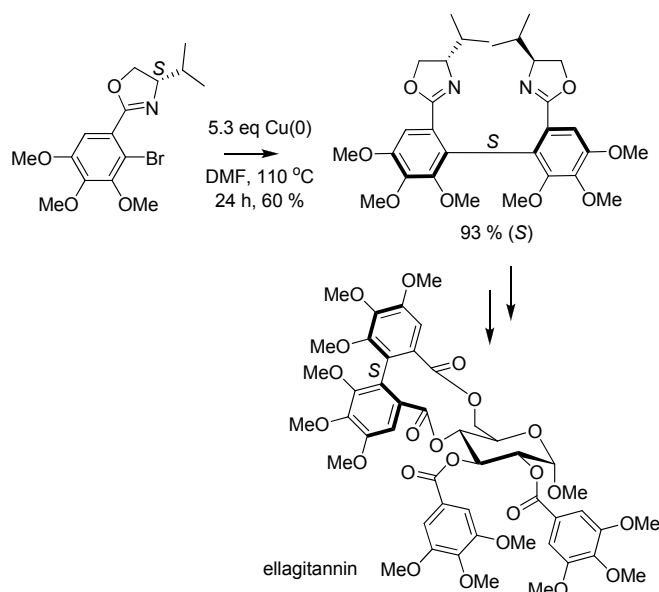
Employing dimethylformamide (DMF) as solvent and using pre-activated copper powder, which is made from reduction of CuI with potassium, allows this reaction to proceed at lower temperature (about 100 °C).

Mechanistic studies of the Ullmann coupling reveal two possible pathways: (1) through arylcopper intermediates formed by oxidative addition of Cu(0) to aryl halides giving ArCu(II) followed by reduction with Cu(0) to give ArCu(I). The ArCu(I) then oxidatively adds to another molecule of aryl halide affording an Ar-Cu(III)X-Ar reactive intermediate which undergoes reductive elimination to furnish biaryls and Cu(I)X;<sup>31</sup> or (2) *via* Cu(0) initialising the formation of aryl radicals followed by bi-aryl radical coupling to form aryl-aryl bonds<sup>32</sup> (Scheme 1.3.3).



**Scheme 1.3.3** Two possible mechanisms for the Ullmann reaction.

Atropisomerically enriched biaryls can be obtained by introduction of a chiral group on the aryl halides prior to Ullmann-type coupling. For example, Meyers reported formation of various biaryls by Ullmann-type coupling between two (*S*)-oxazoline functionalised aryl bromides. A good diastereomeric ratio (93:7) of the desired (*S*)-biaryl resulted from a steric repulsion by the two isopropyl groups on the two oxazolines in the Aryl<sup>\*</sup>-Cu(III)Br-Aryl<sup>\*</sup> intermediate. The thermodynamically favoured (*S*)-biaryl was obtained after reductive elimination and was applied in the total synthesis of ellagitannins (Scheme 1.3.4).<sup>33</sup>

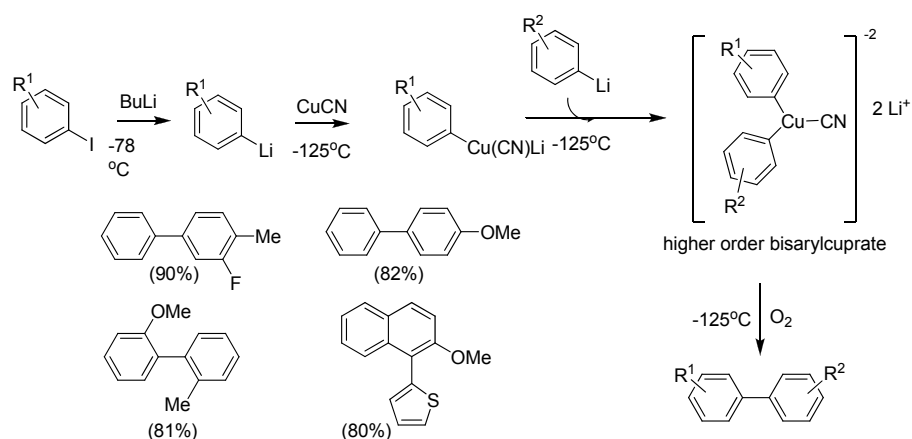


**Scheme 1.3.4** Meyers' asymmetric Ullmann-type biaryl coupling *en route* to ellagitannin.<sup>33</sup>

Unsymmetrical biaryls can be obtained by direct subsection of carefully-selected aryl halides to optimised Ullmann coupling conditions. A large excess of one aryl halide component is required to achieve good reaction yields. However, difficult to control reaction conditions and tedious purification procedures limit the application of this method in synthesis.<sup>34</sup>

### 1.3.1.2 Unsymmetrical biaryl formation using arylcuprates

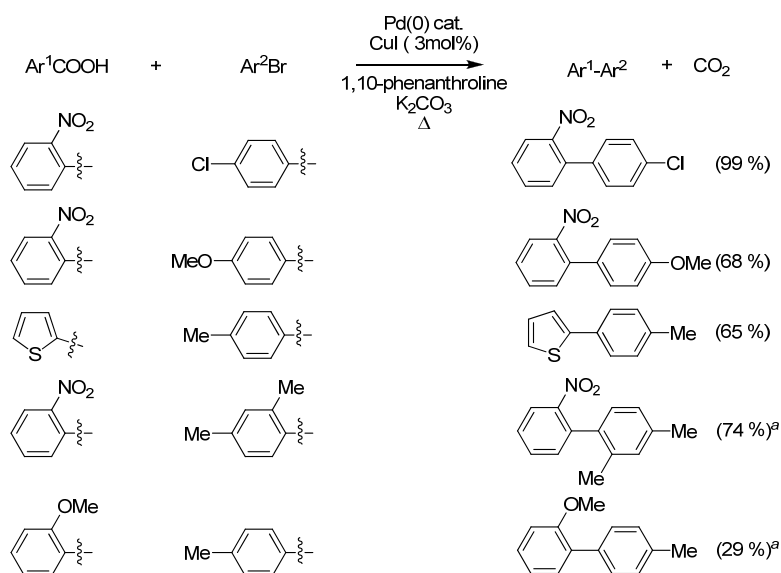
A more practical strategy for unsymmetrical biaryl formation using bisarylcuprates was reported by Lipshutz in 1993. By employing two pre-formed aryllithium reagents sequentially and a stoichiometric amount of Cu(I)CN at low temperature, a higher order (H.O.) bisarylcuprate  $[\text{Ar}^1\text{Ar}^2\text{Cu}(\text{CN})\text{Li}_2]$  intermediate was formed which upon *in situ* oxidation with a molecule of oxygen gave the desired biaryls. Electron-rich, neutral, sterically hindered and heterocyclic biaryls were prepared by this method in excellent yields (Scheme 1.3.5).<sup>35</sup>



**Scheme 1.3.5** Lipshutz's method for the synthesis of unsymmetrical biaryls by oxidative coupling of *in situ* generated of H.O. bisarylcuprates.<sup>35</sup>

### 1.3.1.3 Decarboxylative coupling

More recently, Gooßen has developed a more concise and convenient catalytic biaryl coupling method by employing arylcarboxylic acids and CuI to achieve Pd(0) catalysed decarboxylative cross-coupling with aryl bromides at elevated temperature (Scheme 1.3.6).<sup>36</sup>

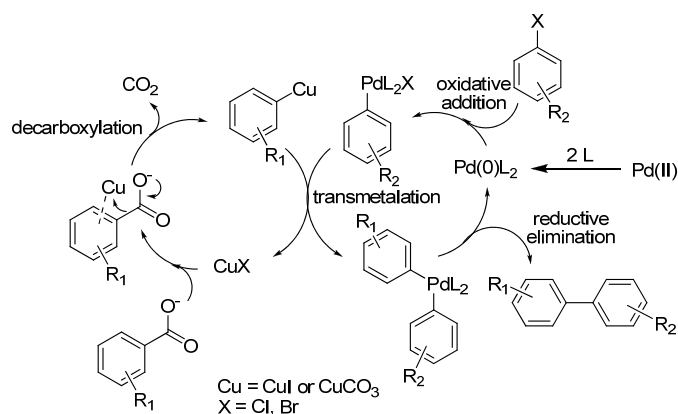


<sup>a</sup> employing  $\text{CuCO}_3$  (1.5 eq), KF (2 mol%) instead

**Scheme 1.3.6** Gooßen's Copper-mediated decarboxylative cross-coupling catalysed by Pd(0).<sup>36</sup>

Biaryls were formed in good to quantitative yields when electron-deficient and heteroaromatic carboxylic acids were coupled with electron-deficient and electron-rich aryl bromides. Cross-coupling of sterically demanding aryl bromides required excess  $\text{CuCO}_3$  and the use of  $\text{KF}$  as an additive. However, electron-rich arylcarboxylic acids gave inferior yields even when using excess  $\text{CuCO}_3$ .

Mechanistic studies revealed that  $\text{CuI}$  directly facilitated decarboxylation of the arylbenzoate salts to give reactive arylcopper intermediates ( $\text{ArCu}$ ) which immediately undergo transmetalation with the arylpalladium species derived from  $\text{Pd(0)}$  oxidative addition to the aryl halide. Upon reductive elimination, biaryls are obtained with regeneration of  $\text{Pd(0)}$  (Scheme 1.3.7).<sup>37</sup>



**Scheme 1.3.7** The proposed mechanism for Gooßen's decarboxylative cross-coupling reaction.<sup>37</sup>

As both the copper salt and  $\text{Pd(0)}$  are administered in just catalytic amounts for most substrates,  $\text{CO}_2$  is the only by-product from the reaction and no pre-formed organometallic coupling partners are required, this direct decarboxylative cross-coupling method is suited to industrial scale biaryl-forming processes.

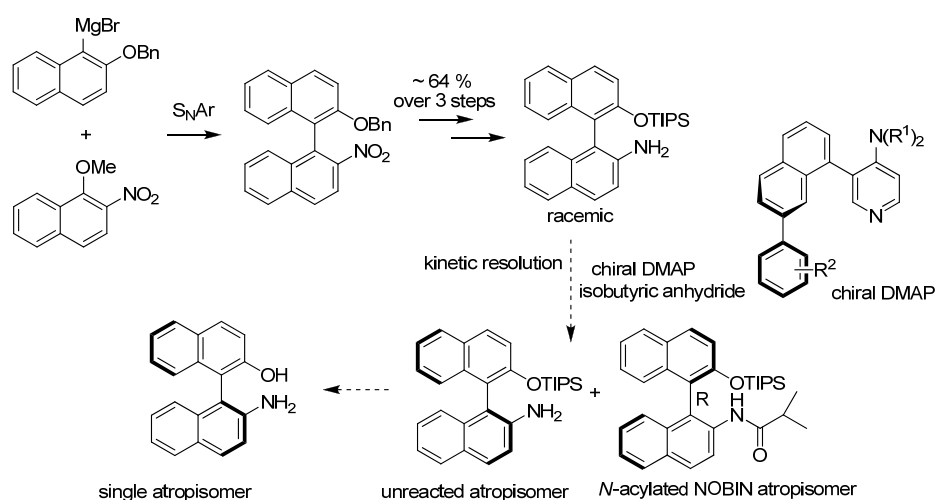
### 1.3.2 Biaryl formation by nucleophilic aromatic substitution ( $\text{S}_{\text{N}}\text{Ar}$ )

Aryl halides cannot participate in direct bimolecular nucleophilic substitution ( $\text{S}_{\text{N}}2$ ) reactions as aliphatic halides can. Instead, aryl halides and certain other aryls containing electron-withdrawing groups (*e.g.*  $\text{NO}_2$ , oxazoline, ester, sulfonyl) at the *ortho*- and/or *para*-positions can participate in nucleophilic substitution reactions through a stepwise addition-elimination mechanism. The addition-elimination process is referred to as the  $\text{S}_{\text{N}}\text{Ar}$  reaction mechanism. The addition of the

nucleophile to the electron-deficient aromatic ring at the *ipso*-position of the halide substituent is usually the rate-determining step and so is particularly favoured the following order: F > Cl > Br > I.

By employing aryllithium or aryl Grignard reagents as the nucleophile, biaryls can be prepared by this route. With the introduction of a suitable chiral auxiliary on the substrates, axial chirality of the biaryl can be controlled.<sup>38</sup> For example, Hattori has described a method for the preparation of racemic NOBIN derivatives by S<sub>N</sub>Ar using a naphthyl Grignard reagent and 1-alkoxy-2-nitronaphthalene. However, employing an optically pure menthoxyl chiral auxiliary in place of the methoxy group an asymmetric S<sub>N</sub>Ar reaction resulted to give the product in moderate yield (51 %) and enantioselectivity (78 % *ee*).<sup>39</sup>

Our group is currently developing a potentially more efficient approach for the preparation of enantiomerically enriched NOBIN by employing an axial chiral DMAP to effect a kinetic resolution of racemic NOBIN prepared by Hattori's method (Scheme 1.3.8).

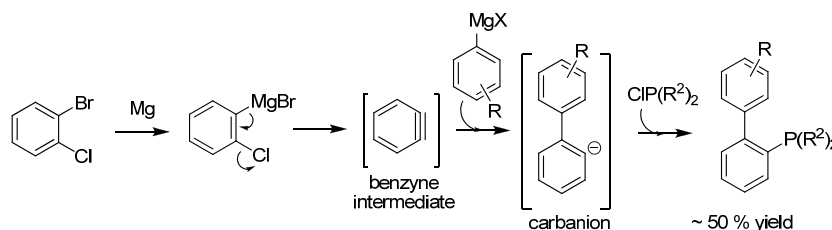


**Scheme 1.3.8** Spivey's approach to the resolution of NOBIN prepared by an achiral S<sub>N</sub>Ar reaction.

### 1.3.3 Biaryl formation *via* aryne intermediates

Arynes such as benzyne are generally generated by elimination of a suitable leaving group *ortho* to a carbanion on an aromatic system. The aryne intermediates are highly reactive towards nucleophilic addition to furnish substituted aromatics and

can be used to form biaryls. Buchwald introduced a concise and practical method for the preparation of dialkylbiaryl phosphine ligands through a benzyne intermediate. The benzyne intermediate was generated by direct formation of the Grignard reagent from 2-bromochlorobenzene followed by elimination of chloride after which the benzyne was trapped by another aryl Grignard reagent giving a biaryl carbanion and then sequentially reacted with chlorodialkylphosphine to furnish the desired biaryl phosphine ligands in moderate overall yields (Scheme 1.3.9).<sup>40</sup>



**Scheme 1.3.9** Buchwald's procedure for the preparation of dialkylbiaryl phosphine ligands.<sup>40</sup>

This procedure has been applied on a multi-kilogram scale for commercialisation of the Buchwald ligands.

## 1.4 Molecular imaging chemistry

Molecular imaging refers to multidisciplinary technologies encompassing medicine, chemistry, pharmacology and nuclear medicine to monitor and visualise living biological subjects in real time. Molecular imaging generally involves administering specific biomarkers or radiolabelled tracers into living organisms for characterisation and quantification of biological processes or for pathological diagnosis at the cellular or subcellular level by tomographic image generation.<sup>41</sup>

There are several modalities that are currently used for molecular imaging such as computed tomography with X-rays (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), optical imaging and ultrasound examination. These technologies are non-invasive, high resolution procedures that can be employed in routine operations which are widely used for clinical diagnosis, pathological research and recently in new drug development.<sup>42</sup> By combining tomographic technologies (*e.g.* PET-CT, SPECT-CT and PET-MRI), real time detection at the molecular or cellular level with

high spatial resolution is possible. To elaborate biological processes more precisely in living subjects, high affinity, target-directed biomarkers or radioactive ligands are essential and the development of these relies on synthetic chemistry.

The basic concepts and recent advances in PET and SPECT are briefly described in the following section. Development of synthetic radiolabelling methodology will be discussed in Chapter 3 of this thesis.

### 1.4.1 Basic concept and advances in PET

PET scanning was first achieved by Kuhl and Edwards in 1964.<sup>43</sup> PET requires a radiolabelled imaging agent containing nuclei that decay by emission of a positron ( $\beta^+$ ). The emitted positron only travels a certain short distance in tissues before being annihilated with an electron to produce two photons with 511 keV energy. These  $\gamma$ -rays radiate in opposite directions ( $180^\circ \pm 0.25^\circ$ ). Detection of the two  $\gamma$ -rays generated simultaneously from positron annihilation by an array of detectors followed by coincidence processing allows image reconstruction and display on a screen (Figure 1.4.1).

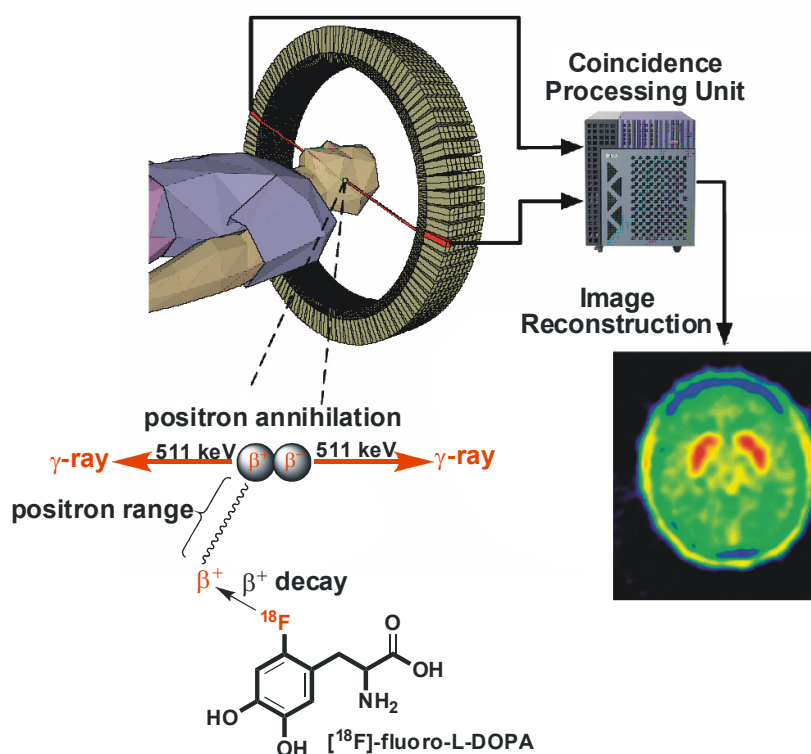


**Figure 1.4.1** PET processing (the image was reproduced and modified from the original source).<sup>44</sup>

The probe molecules for PET scanning are normally positron decay nuclei labelled pharmaceuticals. The radioisotopes generally used for direct replacement of a cold nucleus in a commercial drug are  $^{11}\text{C}$ ,  $^{14}\text{O}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$  and  $^{124}\text{I}$ . The isotopic replacement has no significant affect on the physicochemical and pharmacokinetic properties of the drug. As there is no positron emitting isotope of hydrogen, substitution of a hydrogen atom or a hydroxyl group with the  $^{18}\text{F}$  isotope is a common tactic. The fluorine atom has similar van der Waal's radius as a hydrogen atom (1.35 Å *cf.* 1.20 Å respectively), so no critical steric effects result from the fluorine-hydrogen replacement. However, as fluorine is the most electronegative atom, electronic and lipophilic characteristics of the F-replaced pharmaceutical are altered.

Pharmacological studies indicate that the affinity of F-replaced drugs for certain targets may be enhanced due to their decreased lipophilicity as compared to the parent compound in certain cases. In addition, the  $^{18}\text{F}$  isotope emits positron of low energy resulting in a short positron range and consequently high spatial resolution. The half-life ( $t_{1/2}$ ) of the  $^{18}\text{F}$  isotope is 109 minutes which allows multistep chemical transformations for compound preparation and relative long tracing time *in vivo* (Table 1.4.1).<sup>45</sup>

| Nuclei           | $t_{1/2}$<br>(min) | Maximum<br>energy (MeV) | Mode of decay                             | Example of drugs and its specific<br>applications                                           |
|------------------|--------------------|-------------------------|-------------------------------------------|---------------------------------------------------------------------------------------------|
| $^{18}\text{F}$  | 109                | 0.64                    | $\beta^+$ (97 %)<br>EC (3 %) <sup>a</sup> | 6- $^{18}\text{F}$ -fluoro-L-DOPA<br>Presynaptic dopaminergic system<br>Parkinson's disease |
| $^{11}\text{C}$  | 20.3               | 0.97                    | $\beta^+$ (99 %)                          | $^{11}\text{C}$ -raclopride<br>Dopamine D <sub>2</sub> /D <sub>3</sub> receptors            |
| $^{13}\text{N}$  | 10                 | 1.20                    | $\beta^+$ (100 %)                         | $^{13}\text{N}$ -cisplatin<br>Glioblastoma; tumour                                          |
| $^{124}\text{I}$ | 4.2 days           | 2.14                    | $\beta^+$ (25 %)<br>EC (75 %)             | $^{124}\text{I}$ -AZGP<br>Tumour hypoxia tracer                                             |
| $^{15}\text{O}$  | 2                  | 1.74                    | $\beta^+$ (100 %)                         | $\text{H}_2^{15}\text{O}$<br>Solid tumour blood perfusion                                   |

<sup>a</sup>Electron capture decay;  $^{124}\text{I}$ -AZGP: [ $^{124}\text{I}$ ]-iodo-azomycin galactopyranoside

**Table 1.4.1** Common radionuclides for PET imaging, examples and applications in living subjects.

The concentration of tracer in tissues required for recording a PET image is in the range 1-10 pM ( $10^{-12}$  mol/L) and PET detection has no depth limit for the radiolabelled probes. PET scanning can also provide quantitative drug concentration data in living subjects. However, low spatial resolution and high expense (due to the requirement for most positron isotopes to be generated *in situ* from a cyclotron) relative to alternative imaging methods limits the current applications of PET. Nevertheless, PET is a powerful tomographic technology in medical research and clinical diagnosis.

### 1.4.2 Molecular imaging with SPECT

The technology for SPECT is similar to PET. The radioisotopes used in SPECT however decay with *direct* emission of  $\gamma$ -rays. These are collected by detectors named gamma-cameras which comprise an array of scintillators converting the emitted  $\gamma$ -rays into visible light. Electronic signals are generated based on the intensity of the visible light which, following image reconstruction, are displayed as tomographic images.

In general, the  $\gamma$ -emitting isotopes for SPECT imaging probes have a longer half-life time than the positron-emitting nuclei used in PET scanning. As a consequence, more sophisticated chemical transformations and modifications from precursor compounds to install the isotope onto pharmaceuticals are possible (Table 1.4.2).

| Nuclei             | $t_{1/2}$ | $\gamma$ energy<br>(keV)               | Examples of drugs and specific applications                    |
|--------------------|-----------|----------------------------------------|----------------------------------------------------------------|
| $^{99m}\text{Tc}$  | 6 h       | 140 (89 %)                             | $^{99m}\text{Tc}$ -DTPA<br>Brain, kidneys                      |
| $^{123}\text{I}$   | 13.2 h    | 159 (83 %)                             | $^{123}\text{I}$ - $\beta$ -CIT<br>Dopaminergic system         |
| $^{201}\text{Tl}$  | 73 h      | 167 (10 %),<br>80 (20 %),<br>71 (47 %) | $^{201}\text{TlCl}$<br>Bronchioloalveolar cell carcinoma (BAC) |
| $^{111m}\text{In}$ | 2.83 d    | 245 (94 %)                             | $^{111m}\text{In}$ -octreotid<br>Somatostatin receptors        |

**Table 1.4.2** Radionuclides for SPECT imaging, examples and applications.

Unlike the high energy  $\gamma$ -rays collected by the PET detector, the SPECT detector is sensitive to low energy  $\gamma$ -rays directly decaying from the radioisotope labelled probe compound. As a result, scattering and attenuation of the signal by the surrounding matrix affects the sensitivity and resolution of SPECT. Therefore, both the sensitivity (10-100 pm *cf.* 1-10 pm) and spatial resolution of SPECT is less than that of PET. However, SPECT-CT hybrid systems are currently being developed which allow these differences to be minimised.

The advantages of SPECT over PET imaging include the lower cost for SPECT imaging and the possibility of using simultaneous multi-isotopic probes for imaging *in vivo*. This is possible because the  $\gamma$ -rays from separated isotopically labelled compounds can be distinguished by their different emission energies. This is not possible for a PET system as the  $\gamma$ -rays from different nuclei have the same emitted energy (Figure 1.4.2).<sup>46</sup>

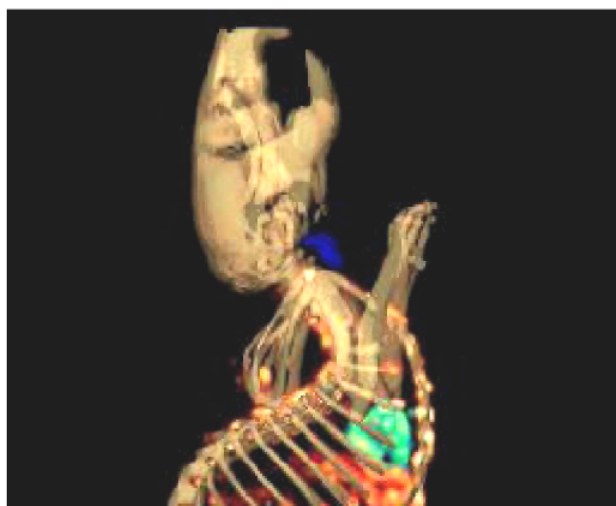


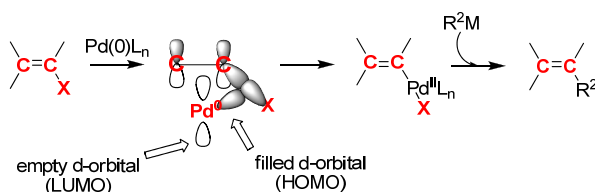
**Figure 1.4.2** Simultaneous multi-isotopic SPECT-CT image of a mouse: the thyroid ( $^{123}\text{I}$ , blue), heart ( $^{201}\text{Tl}$ , green) and bones ( $^{99\text{m}}\text{Tc}$ , orange), co-registered with a CT scan (yellow).<sup>46</sup>

Modern molecular imaging modalities such as PET, PET-CT, SPECT and SPECT-CT provide comprehensive schemes for visualising targets in living subjects and have been adopted by the pharmaceutical industry for smart drug development programmes.

## 2. Development of novel aryl- and alkenyl- cross-coupling reactions based on light fluororous-tagged organogermanes

Transition metal catalysed cross-coupling reactions have been developed and applied to the synthesis of a wide range of aryl-containing compounds such as biaryls and styrenes for several decades. Amongst the transition elements, Pd has the extraordinary ability to catalyse the formation of carbon-carbon bonds between unsaturated centres.<sup>47</sup>

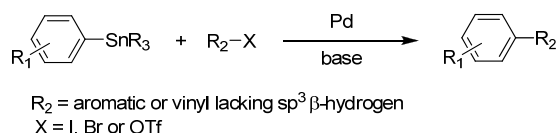
Pd is a late transition metal that forms  $d^8$  and  $d^{10}$  complexes in a low oxidative state that are highly polarisable. Thus, it is categorised as being soft and easily accepts electrons to fill its empty d-orbitals (the LUMO) and therefore performs as a Lewis acid (electrophile). Meanwhile its fully occupied non-bonding d-orbitals (the HOMO) are available to donate electrons as a Lewis base (nucleophile). The dual electronic aptitude of Pd results in high affinity towards non-polarised  $\pi$ -enriched substrates (*e.g.* alkenes, alkynes and arenes) forming  $\pi$ -palladium complexes followed by insertion and cross-coupling reactions (Scheme 2.1.1).<sup>48</sup>



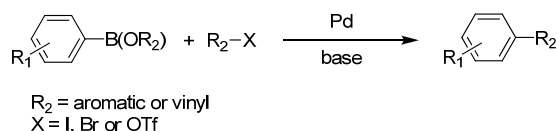
**Scheme 2.1.1** The Dewar-Chatt-Duncanson (DCD) model of  $\pi$ -Pd complexation with an alkenyl halide.<sup>48</sup>

The use of Pd(0)-mediated cross-coupling between aryl halides and pre-formed aryl organometallics has received the most attention. These reactions include the Stille reaction (organostannanes),<sup>49</sup> the Suzuki reaction (organoborates),<sup>50</sup> the Negishi reaction (organozincs),<sup>51</sup> the Hiyama reaction (organosilanes),<sup>52</sup> and the Kumada reaction (Grignard reagents).<sup>53</sup> The Sonogashira reaction<sup>54</sup> and the Heck reaction<sup>55</sup> are related processes for coupling aryl halides with alkynyl and alkenyl components respectively (Scheme 2.1.2).

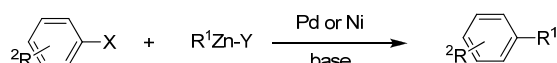
**Stille reaction:** Pd-catalysed cross-coupling reaction between halides and organostannanes



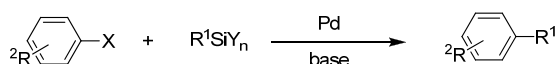
**Suzuki reaction:** Pd-catalysed cross-coupling reaction between halides and organoborons.



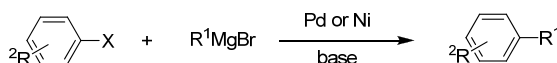
**Negishi reaction:** Pd or Ni-catalysed cross-coupling reaction between halides and organozincs



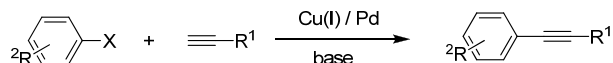
**Hiyama reaction:** Pd-catalysed cross-coupling reaction between halides and organosilanes



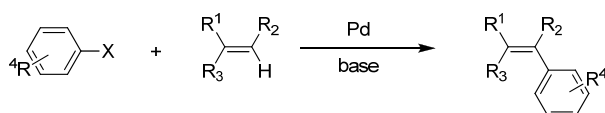
**Kumada reaction:** Pd or Ni-catalysed cross-coupling reaction between halides and Grignard reagents



**Sonogashira reaction:** Cu(I)/Pd-catalysed cross-coupling reaction between halides and terminal alkynes



**Heck reaction:** Pd-catalysed cross-coupling reaction of aryl or vinyl halides and alkenes



**Scheme 2.1.2** Summary of transition metal-catalysed cross-coupling reactions.

In the Negishi reaction, organozincs are used which are moisture sensitive, as are the Grignard reagents used in the Kumada reactions. Although the Suzuki reaction is used widely for cross-coupling reactions because it uses non-hazardous organoboranes as substrates, homo-coupling products often accompany the desired cross-coupling products and in many cases cause difficulties for purification by column chromatography.<sup>56</sup> Even though many organoborane building blocks are commercially available, the preparation and purification of customised organoboranes for coupling purposes is often tedious.

In this section, Pd-mediated cross-coupling reactions involving group 14 elements

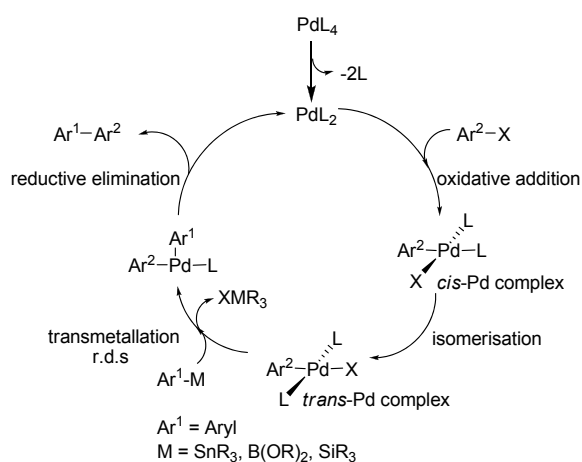
will be reviewed with a focus on advances in organosilane and organogermane based coupling protocols as an alternative approach to the Stille coupling.

## 2.1 Pd-catalysed cross-coupling reactions of organostannanes (The Stille reaction)

Pd-catalysed cross-coupling of organostannanes with aryl- or alkenyl- halides is referred to as Stille coupling. Because organostannanes are stable to moisture and air, and are tolerant to various functional groups, Stille coupling represents a facile method for construction of biaryl or styrenyl systems. The high reactivity of organostannanes in Stille coupling is due to the polarised carbon-tin bond. Therefore, pre-activation of the substrate is not generally required for Stille coupling to take place. However, organostannanes are labile to strong nucleophiles and organolithium reagents and so the organostannane functionality can only be installed in the molecule immediately prior to the coupling step. The main drawbacks of Stille coupling are the toxicity of organostannanes and of the tin-containing by-products, particularly when Stille coupling is used on a large scale.

### 2.1.1 The mechanism the Stille reaction

A general catalytic cycle for aryl-aryl cross-coupling has been proposed (Scheme 2.1.3).<sup>57,58</sup>



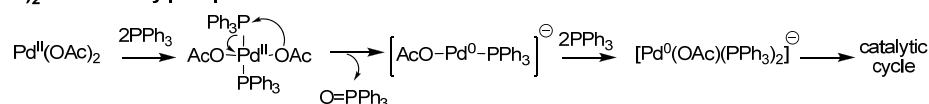
**Scheme 2.1.3.** A general catalytic cycle for Pd(0)-catalysed cross-coupling reactions.<sup>57,58</sup>

Firstly, the pre-catalyst  $\text{PdL}_4$  ( $18e^-$ ) eliminates two ligands to form the nucleophilic  $\text{Pd}(0)$ -catalyst,  $\text{PdL}_2$  ( $14e^-$ ), which reacts with the electrophilic aryl halide through oxidative addition to give a 16-electron *cis*- $\text{Pd}(\text{II})$ -complex which subsequently isomerises to the more stable *trans*- $\text{Pd}(\text{II})$ -complex. The *trans*- $\text{Pd}(\text{II})$ -complex undergoes transmetalation with the organometallic component ( $\text{Ar}^1\text{-SnR}_3$  in the case of the Stille coupling) with concomitant release of the corresponding organometallic halide ( $\text{XMR}_3$ ). This transmetalation step is usually the rate determining step in this catalytic cycle. In the final step of the catalytic cycle, the biaryl is formed *via* a reductive elimination process and the active  $\text{Pd}(0)$ -catalyst is regenerated. These individual steps are examined in more detail below.

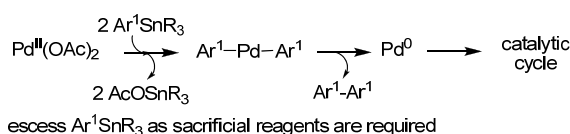
### 2.1.2 Generation of reactive $\text{Pd}(0)$ complexes from $\text{Pd}(\text{II})$ precursors

An 18-electron  $\text{Pd}(0)$  precursor such as  $\text{Pd}(\text{PPh}_3)_4$  is required to participate in the catalytic cycle. Dissociation of two coordinated ligands is necessary to form a reactive 14-electron  $\text{Pd}(0)$  catalyst. There are alternative methods to obtain  $14e^-$   $\text{Pd}(0)$  catalysts *in situ* by reduction of  $\text{Pd}(\text{II})$  pre-catalysts with phosphine ligands,<sup>59,60</sup> sacrificial organometallics<sup>61</sup>, or amines in the reaction mixture (Scheme 2.1.4).

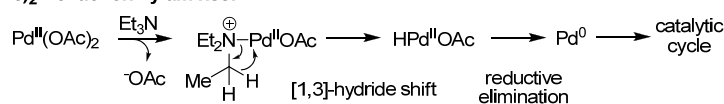
#### $\text{Pd}(\text{OAc})_2$ Reduction by phosphines:



#### $\text{Pd}(\text{OAc})_2$ Reduction by organostannanes:



#### $\text{Pd}(\text{OAc})_2$ Reduction by amines:



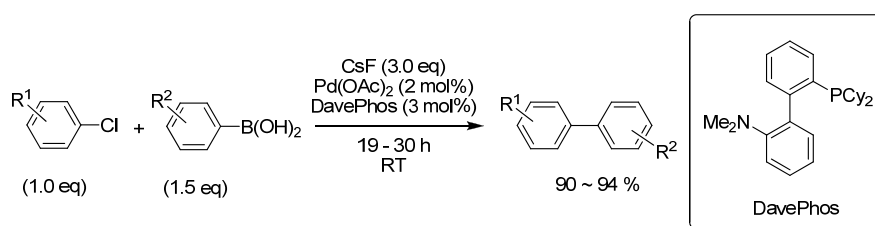
**Scheme 2.1.4.** Examples of *in situ* generation of activated  $\text{Pd}(0)$  from  $\text{Pd}(\text{II})$  pre-catalysts.

Most  $\text{Pd}(\text{II})$  pre-catalysts are bench-stable reagents and more stable to air than their  $\text{Pd}(0)$  congeners. Consequently, employing  $\text{Pd}(\text{II})$  pre-catalysts for coupling reactions is a routine procedure.

### 2.1.3 The oxidative addition

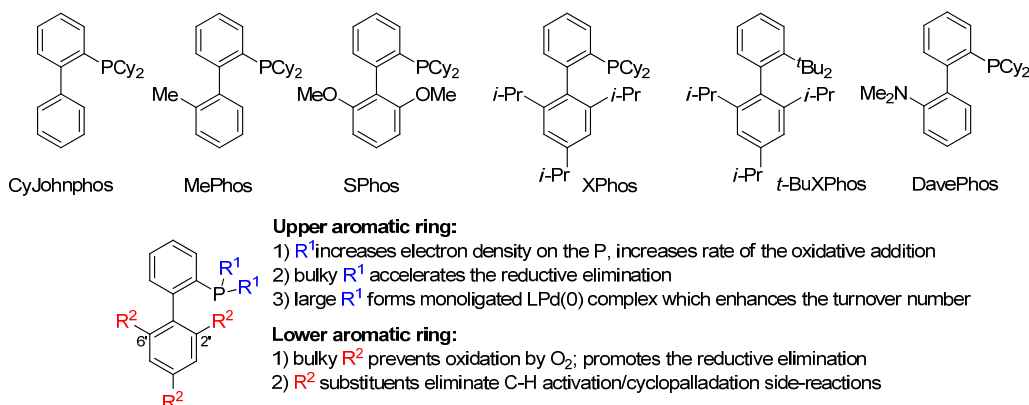
Pd(0) complexes are nucleophilic and undergo oxidative addition with aryl halide or aryl pseudohalide electrophiles to give a 16-electron Pd(II)-complexes. The rate of oxidative addition follows the order: Ar-I > Ar-OTf  $\approx$  Ar-Br  $\gg$  Ar-Cl. Although aryl chloride building blocks are more readily available and cost less than the corresponding bromides, iodides and triflates, they are not often appropriate coupling partners for practical chemistry due to their sluggish oxidative addition rate, however appropriate choice of ligands can help in this regard (*vide infra*).

For example, Buchwald has developed some highly reactive Pd(0) catalytic systems by introducing dialkylbiaryl phosphines as ligands to achieve the Suzuki coupling of non-activated aryl chlorides with arylboronic acids to give biaryls in excellent yields at room temperature (Scheme 2.1.5).<sup>62</sup>



**Scheme 2.1.5.** Buchwald's Suzuki coupling with aryl chlorides using DavePhos as ligand.<sup>62</sup>

These bulky, strongly  $\sigma$ -donating phosphine ligands coordinate to Pd(0) resulting in an electron-rich Pd(0) centre which facilitates oxidative addition. The principles used for designing of these biaryl ligands and the functions of the substituents have been elaborated by Buchwald (Scheme 2.1.6).<sup>29</sup>



**Scheme 2.1.6.** Buchwald's dialkylbiaryl phosphine ligands and the functions of their structural features.<sup>29</sup>

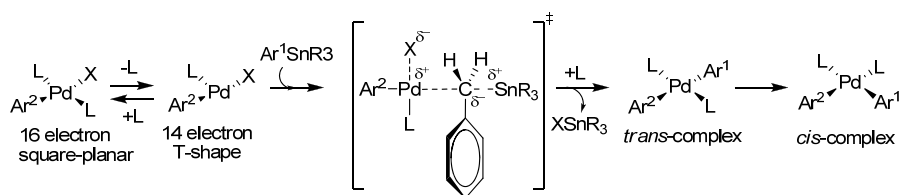
Although the dialkylbiaryl phosphine ligands were initially designed for Suzuki coupling, these versatile ligands are compatible and profitable for other cross-coupling protocols catalysed by palladium including amination of aromatic rings because these protocols have similar catalytic cycles.<sup>63</sup>

Aryl pseudohalides are alternative coupling partners. Pseudohalides include: triflate (OTf), nonaflate (ONf), methanesulfonate (OMs), 4-toluenesulfonate (4-TsO) and diazonium salts ( $N_2^+$ ). Amongst these, organotriflates are the most commonly used in Pd-catalysed cross-coupling reactions. However, the reactivity of aryl triflates towards oxidative addition of Pd(0) differs from aryl halides and addition of LiCl is often essential.<sup>64</sup> Comprehensive studies on additives for coupling with organotriflates indicated that LiCl can either accelerate or retard reaction rates by various mechanisms.<sup>65,66</sup> The effect of LiCl on the catalytic cycle is discussed in the following section.

#### 2.1.4 The transmetalation

The transmetalation step is the second step of the cross-coupling catalytic cycle and usually the rate-determining step of the whole processes. There are two proposed mechanisms: dissociative and associative.

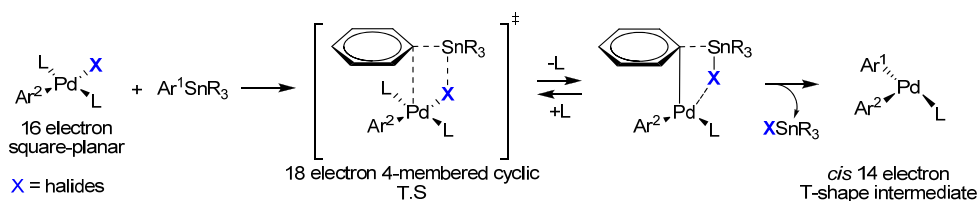
In the dissociative pathway, the 16 electron Pd(II) complex eliminates a ligand to form a 14 electron T-shape Pd(II) complex prior to transmetalation with an arylstannane. The arylstannane acts as a nucleophile towards the 14 electron Pd(II) complex with concomitant electrophilic cleavage of the C-Sn bond. This is described as an  $S_E2$  transition state mechanism. This mechanism produces a *trans* Pd(II) complex which is isomerised into a *cis* conformation for reductive elimination. The *trans*-to-*cis* isomerisation process is achieved by a dissociative mechanism *via* the T-shape intermediate. The  $S_E2$  transmetalation dissociative pathway was originally proposed by Stille (Scheme 2.1.7).<sup>61</sup>



**Scheme 2.1.7.** Stille's proposed dissociative mechanism for transmetalation through a 14-electron T-shaped intermediate.<sup>61</sup>

Although the dissociative pathway through a 14-electron, three-coordinate complex has been observed commonly in Pt chemistry,<sup>67</sup> the evidence in the case of Pd is not compelling and as a result Espinet has proposed a transmetalation step which goes through an associative pathway.<sup>56,66</sup> In the associative pathway, the 16 electron Pd(II) complex interacts with the arylstannane nucleophile *via* either a cyclic or an open transition state to generate the  $\text{Ar}^1\text{Ar}^2\text{PdL}_2$  complex.

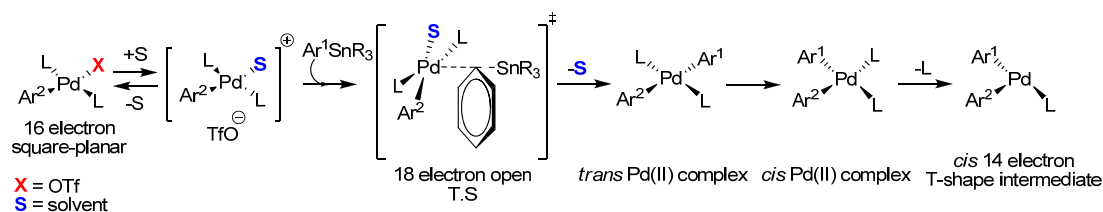
The cyclic transition state is preferred when the X substituent is a halide in a moderately coordinating solvent. The strong coordination between the halide and the  $\text{SnR}_3$  group polarises the C-Sn bond and enhances the nucleophilicity at the *ipso*-carbon of the arylstannane. A 4-membered cyclic transition state is formed which facilitates the transmetalation. The structural features of the cyclic transition state are the retention of configuration at the *ipso*-position of  $\text{Ar}^1$  and the *cis* geometry between the  $\text{Ar}^1$  and  $\text{Ar}^2$  groups. Therefore, the *cis*  $\text{Ar}^1\text{Ar}^2\text{PdL}_2$  intermediate yielded by the 4-membered cyclic transition state is ready for the subsequent reductive elimination to furnish biaryls (Scheme 2.1.8).<sup>68</sup>



**Scheme 2.1.8.** Espinet's proposed associative mechanism for transmetalation through a 4-membered cyclic transition state.<sup>68</sup>

The open transition state associative pathway is favoured when the X substituent of the  $\text{Ar}^2\text{Pd}^{\text{II}}\text{L}_2\text{X}$  complex is triflate (OTf) for example, in a polar solvent (*e.g.* DMF or NMP). A solvato  $[\text{Ar}^2\text{Pd}^{\text{II}}\text{L}_2\text{S}]\text{OTf}$  complex is formed which interacts with the arylstannane *via* an associative 5-coordinate open transition state allowing the  $\text{Ar}^1$  group to replace the solvent ligand giving a *trans*  $\text{Ar}^1\text{PdAr}^2\text{L}_2$  complex which is

subsequently isomerised into a *cis*  $\text{Ar}^1\text{Ar}^2\text{PdL}_2$  species (Scheme 2.1.9).<sup>68</sup>

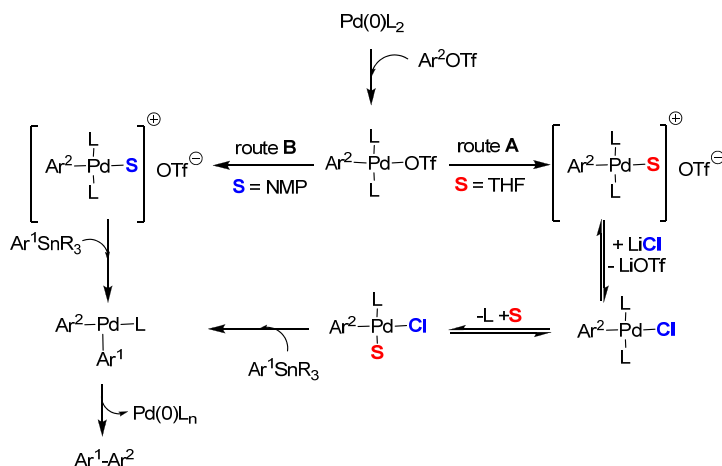


**Scheme 2.1.9.** Espinet's proposed associative mechanism for transmetalation through an open transition state.<sup>68</sup>

As indicated above, cross-coupling of aryl triflates ( $\text{Ar}^2\text{OTf}$ ) with organostannanes can be promoted by employing LiCl as additive.<sup>64</sup> However, Farina noted that the addition of LiCl to Stille reactions with organic triflates can enhance or inhibit their progress.<sup>65,66</sup>

Espinet has investigated the effect of LiCl on Stille coupling of aryl triflates. In weakly coordinating solvents (*e.g.* THF) and in the absence of LiCl, the rate-determining step of the catalytic cycle is oxidative addition of Pd(0) to the  $\text{Ar}^2\text{OTf}$  furnishing an  $\text{Ar}^2\text{Pd}^{\text{II}}\text{L}_2\text{OTf}$  complex which subsequently forms a solvato  $\text{Ar}^2\text{Pd}^{\text{II}}\text{L}_2(\text{THF})$  intermediate. This intermediate is reluctant to participate in the following transmetalation step. LiCl promotes this step by rapidly displacing the solvent ligand to give a more reactive  $\text{Ar}^2\text{Pd}^{\text{II}}\text{L}_2\text{Cl}$  intermediate (route A, Scheme 2.1.10).

By contrast, in highly polar, strongly coordinating solvents (*e.g.* NMP), the solvato  $\text{Ar}^2\text{Pd}^{\text{II}}\text{L}_2(\text{NMP})$  complex rapidly undergoes transmetalation with organostannanes. Therefore, LiCl is normally not required for coupling organotriflates in strongly coordinating solvents (route B, Scheme 2.1.10).<sup>69,70</sup>



**Scheme 2.1.10.** Espinet's proposed mechanism of coupling with aryl triflates and the involvement of LiCl in different solvent systems.<sup>69</sup>

Hartwig has proposed that LiCl enhances the rate of oxidative addition by increasing the dielectric constant of the reaction media. This can also explain why LiCl is not a promoter for reactions in highly polar solvent systems.<sup>71</sup>

### 2.1.5 The reductive elimination

The reductive elimination is the final step of the catalytic cycle to furnish the desired biaryls or cross-coupling products. The *cis* 14-electron T-shape  $\text{Ar}^1\text{Ar}^1\text{PdL}$  intermediate produced from associative transmetalation *via* cyclic or open transition states is required for reductive elimination. This step is promoted by polar media which are able to stabilise the *cis* T-shape intermediate and facilitate *trans*-to-*cis* isomerisation. In addition, the dissociation of a ligand from the  $\text{Ar}^1\text{Ar}^2\text{PdL}_2$  complex to give the T-shape  $\text{Ar}^1\text{Ar}^2\text{PdL}$  species is believed to be the rate-determining step of the reductive elimination process.<sup>72</sup>

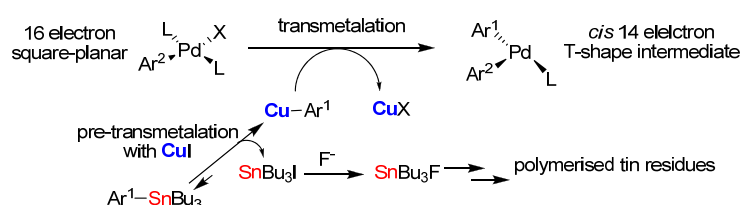
Employing bulky electron-rich ligands such as dialkylbiaryl phosphine ligands is beneficial for both oxidative addition and reductive elimination steps.<sup>29</sup> The advantages of using bulky electron-rich ligands can be attributed to steric<sup>73</sup> and electronic<sup>74</sup> effects.

The efficiency of reductive elimination to afford biaryls is sensitive to the electron density of the two aromatics and the  $\sigma$ -donating behaviour of the ligand on the Pd(II) intermediate. Hartwig concluded that more electron rich aromatics on the Pd(II)

complex facilitate the reductive elimination as does a significant electronic difference between the two aromatics undergoing reductive elimination. Additionally, strong  $\sigma$ -donating ligands on the  $\text{Ar}^1\text{Ar}^2\text{PdL}$  complex induce a concerted reductive elimination more rapidly than weak  $\sigma$ -donating ligands.<sup>74</sup>

### 2.1.6 The role of copper additives

The addition of CuI as a co-catalyst to enhance the rate of Stille cross-coupling reactions was first mentioned by Marino in 1988,<sup>75</sup> and the ‘copper effect’ has been investigated by Farina,<sup>76</sup> Espinet<sup>77</sup> and Baldwin.<sup>78</sup> This effect is now believed to accrue from the formation of a reactive arylcuprate intermediate ( $\text{Ar}^1\text{Cu}$ ) from the corresponding arylstannane prior to Cu to Pd transmetalation in highly polar solvents such as DMF and NMP (Scheme 2.1.11).



**Scheme 2.1.11.** Baldwin's Sn to Cu pre-transmetalation prior to Cu to Pd transmetalation for the Stille coupling in the presence of CuI.<sup>78</sup>

In particular, the synergistic effect of CuI and  $\text{F}^-$  in cross-coupling as described by Baldwin seems to be practically efficient.<sup>78</sup>

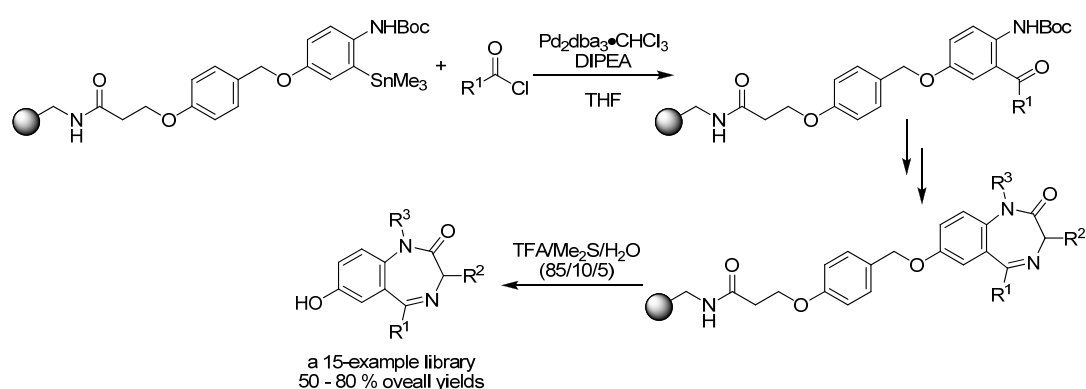
### 2.1.2 Phase-tagged organostannanes in cross-coupling reactions

Transition metal catalysed cross-coupling reactions for stitching building blocks together and increasing molecular complexity have been repeatedly demonstrated to be synthetically valuable. By merging recent developments in SPOS with palladium catalysed cross-coupling reactions, phase-tagged cross-coupling strategies provide for rapid elaboration of biaryl libraries and natural products.

Metal-catalysed SPOS cross-coupling reactions encompass (1) tagged-electrophiles (organic halides); (2) tagged-nucleophiles (organometallics) and (3) tagged-transition

metal catalysts. Employing phase-tagged organostannanes for Stille coupling reactions is attractive in view of the toxicity and tedious purification of the reagents in solution. The latter two phase-tagged methods provide the possibility to recycle and regenerate tagged-coupling partners or catalysts.<sup>79</sup>

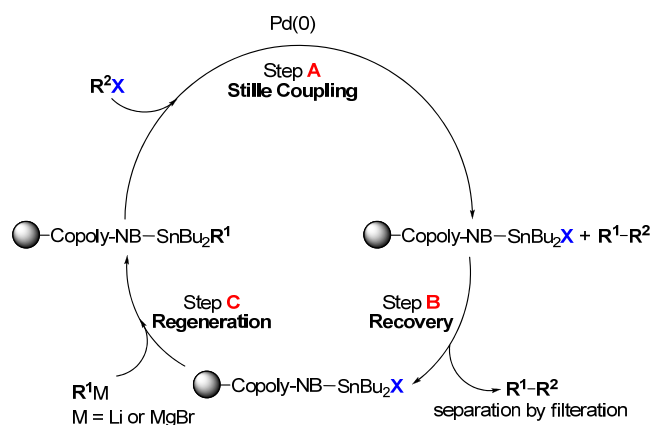
The first phase-tagged Stille coupling was reported in 1994 by Deshpande who coupled polymer-supported aryl iodides with organostannanes with a catalytic amount of Pd(0) and AsPh<sub>3</sub> to give the desired products in excellent yields.<sup>80</sup> Ellman also demonstrated Stille coupling between polymer-supported arylstannanes and acyl chlorides *en route* to a 1,4-benzodiazepine library (Scheme 2.1.12).<sup>81</sup>



**Scheme 2.1.12.** Ellman's SPOS of 1,4-benzodiazepine derivatives using Stille coupling.<sup>81</sup>

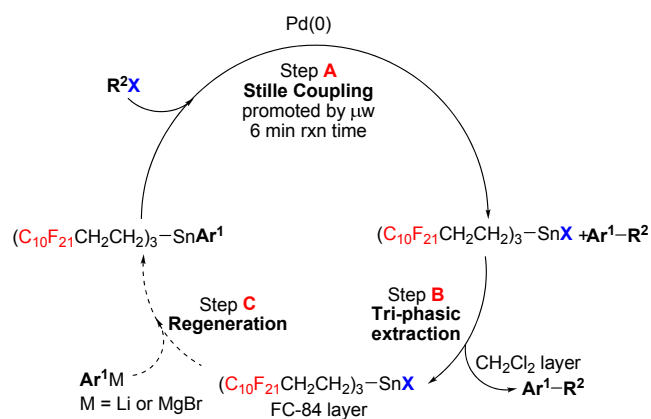
However, these two approaches have drawbacks accruing from the formation of hazardous tin waste which requires further treatment. Several methods were developed to graft organostannanes onto polymer supports,<sup>82,83</sup> fluorous phases<sup>84</sup> and ionic liquids and allow traceless cleavage to yield the expected organic products whilst the toxic and environmentally hazardous tin-containing moieties were retained on the phase tags.

Espinet developed co-polymerised norbornenyl (copoly-NB) grafted with dialkylstannanyl chloride as a precursor for cross-coupling. The products were separated by simple filtration and the remaining copoly-NB bound tin halide was recycled and regenerated for further applications. The tin content in solution was found on average to be just 0.04 % by weight over 5-coupling cycles (Scheme 2.1.13).<sup>83</sup>



**Scheme 2.1.13** Espinet's recyclable polymer-supported organostannanes for Stille coupling.<sup>83</sup>

Fluorous phase tagging has also been applied for Stille coupling. For example, Curran coupled heavy fluorous-tagged organostannanes with organic halides assisted by microwave irradiation to yield the desired products in good yield and in short reaction times. Purification was performed by tri-phasic fluorous liquid-liquid extraction (F-LLE) with water,  $\text{CH}_2\text{Cl}_2$  and FC-84<sup>®</sup>. The non-fluorous organic compounds were retrieved from the  $\text{CH}_2\text{Cl}_2$  layer, the fluorous-tagged tin halide by-products were contained in the FC-84<sup>®</sup> layer, and the inorganic salts resided in the water layer (Scheme 2.1.14).<sup>84</sup>



**Scheme 2.1.14** Curran's fluorous-tagged organostannanes for the Stille coupling and separation by tri-phasic F-LLE.<sup>84</sup>

The tagged-tin moieties retained in the FC-84<sup>®</sup> were anticipated to be able to be recovered and regenerated, although the authors did not report this.

Stille cross-coupling pervades many academic research fields for the construction complex molecules from simple building blocks. In spite of the efforts expended to immobilise organostannane coupling partners onto phase-tags in order to minimise

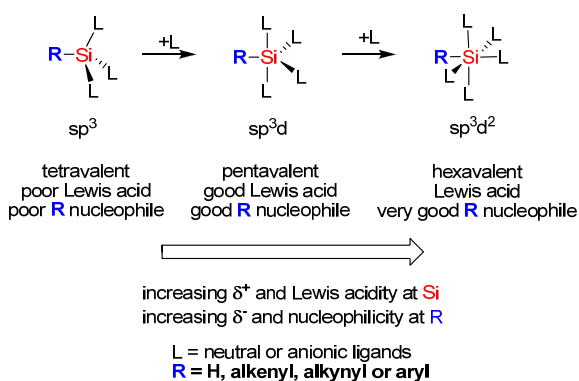
tin contamination, safety issues limit application of the methods in large scale pharmaceutical production. Consequently, alternative non-hazardous, low-cost and versatile organometallics for cross-coupling are in high demand.

## 2.2 Pd-catalysed cross-coupling reactions of organosilanes

In contrast to organostannanes, organosilanes are non-toxic and bench-stable reagents which can act as nucleophiles in cross-coupling with aryl and alkenyl electrophiles to furnish biaryls, styrenes and polyalkenes. This methodology was pioneered by Hiyama<sup>85</sup> and Denmark<sup>86</sup> and is often known as Hiyama-Denmark cross-coupling.

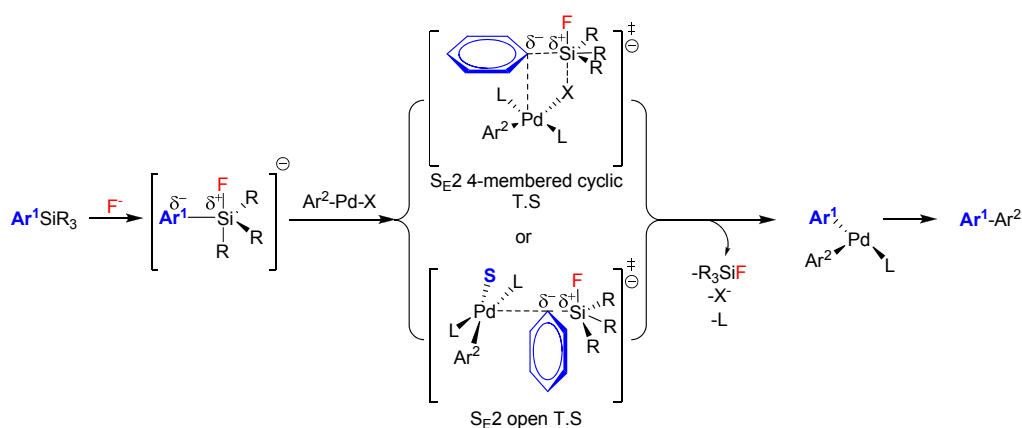
Hiyama-Denmark cross-coupling occurs *via* a similar catalytic cycle (oxidative addition, transmetalation and reductive elimination) to that described for Stille coupling. However, in contrast to the polarised C-Sn bond in organostannanes which undergoes facile transmetalation with an  $\text{Ar}^2\text{PdLX}$  complex, the C-Si bond in organosilanes is less polarized and so tetravalent organosilanes are resistant to transmetalation.

To enhance the reactivity of organosilanes in cross-coupling and allow their application in synthesis, Hiyama first recognised that nucleophilic promoters were required to render appropriate substrates hypervalent and hence more susceptible to cross-coupling. The extracoordination ability of Si results from the vacant 3d orbitals which can mix with the valence shell electrons to form  $\text{sp}^3\text{d}$  and  $\text{sp}^3\text{d}^2$  hybridisations. These hybrid orbitals accommodate extra bonds to the Si centre giving penta- and hexavalency, respectively. The pivotal hypervalency of Si dominates the reactivity of Si-complexes by altering the electron density of the Si centre. The Lewis acidity of the Si centre is proportional to the hypervalency. The less s character in the hybridisation of the Si, the stronger the Lewis acidity. These structural and reactivity features are illustrated below (Scheme 2.2.1).<sup>87</sup>



**Scheme 2.2.1** Structural and reactivity features of hypervalent Si complexes.<sup>87</sup>

Organosilanes can be activated by anionic nucleophiles such as tetrabutylammonium fluoride (TBAF), tetramethylammonium fluoride (TMAF), tris(dimethylamino)sulfonium trimethyldifluorosilicate (TASF), CsF, KF, potassium trimethylsilanolate (KOTMS), Ag<sub>2</sub>O, NaOH and even Cs<sub>2</sub>CO<sub>3</sub>. Due to the strong Si-F bond (560 kJ/mol), fluoride ions generally provide the highest yield of cross-coupling products. Transmetalation is generally believed to be the rate-determining step in Hiyama-Denmark cross-coupling and this step proceeds *via* either an S<sub>E</sub>2 four-membered cyclic or an S<sub>E</sub>2 open transition state (Scheme 2.2.2).<sup>88,89</sup>

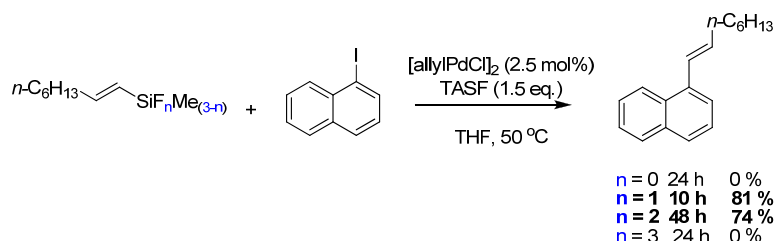


**Scheme 2.2.2.** Proposed pathways for transmetalation during Hiyama-Denmark cross-coupling promoted by fluoride ions.<sup>88,89</sup>

There are various strategies for preparation of organosilane derivatives that can act as substrates for *in situ* activation and sequential cross-coupling to furnish the desired products.

### 2.2.1 Fluoride promoted reactions

In 1989, Hiyama first reported examples of fluoride ion promoted cross-coupling of various alkenyl- and alkynyl trimethylsilanes with aryl and alkenyl halides in good yields.<sup>85</sup> However, inferior outcomes were obtained when attempting to couple styrenyl- and allyl trimethylsilanes with organic halides. Hiyama therefore introduced alkenyl fluoromethylsilanes as substrates for Pd-catalysed cross-coupling reactions activated by fluoride ions. He studied the influence of the fluoro-substituent on the Si centre. Alkenyl monofluorodimethylsilanes were found to be more effective coupling substrates than the corresponding difluoromonomethylsilanes. Additionally, trimethyl- and trifluorosilanes were chemically inert towards the cross-coupling conditions (Scheme 2.2.3).<sup>90</sup>

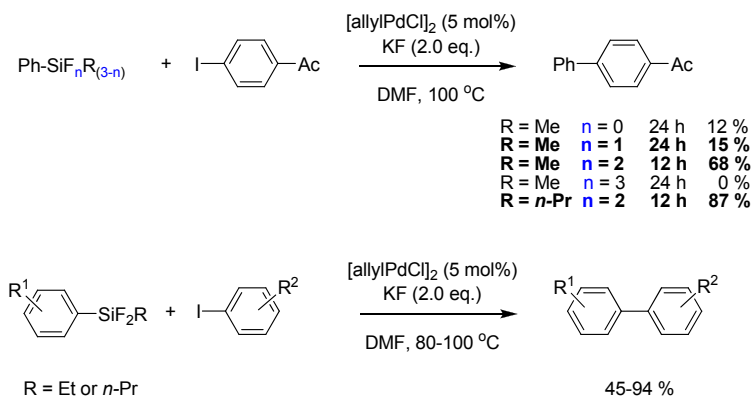


**Scheme 2.2.3.** Hiyama's of cross-coupling of alkenyl fluorosilanes with 1-iodonaphthalene and the influence of fluoro-substituents.<sup>90</sup>

Hiyama applied this method for aryl-aryl bond formation by employing aryl fluoromethylsilanes and aryl iodides in the presence of a fluoride ion source. Coupling of less active aryl fluorosilanes with aryl iodides required a higher loading level of Pd-catalyst and elevated temperatures in comparison with alkenyl-type coupling conditions. The optimised conditions for aryl fluorosilane cross-coupling with organic iodides can be summarised as follows: (1) two fluoro-substituents on Si are essential; (2) fluoride ions are important for coupling efficiency, and (3) using untransferable ethyl- or propyl groups on the Si centre gives better results than methyl analogues. A noticeable amount of methylated aryl by-product was found when aryl difluoromethylsilane was used for cross-coupling, whereas ethyl- and propyl derivatives gave biaryl product exclusively. Trifluorosilanes were completely inactive as had been observed in coupling with alkenyl derivatives.

The scope of this method was demonstrated by cross-coupling  $\text{ArSiF}_2\text{Et}$  and  $\text{ArSiF}_2^i\text{Pr}$  with various aryl iodides giving biaryls in moderate to excellent yields

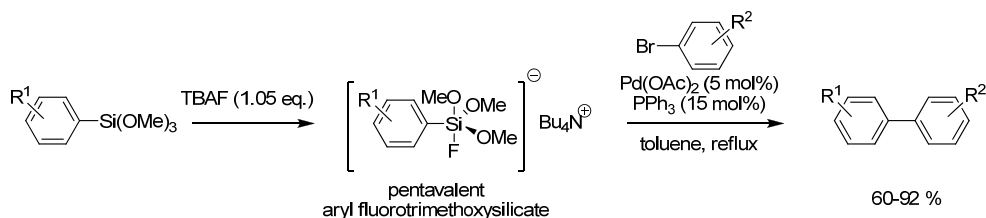
(Scheme 2.2.4).<sup>91</sup>



**Scheme 2.2.4.** Hiyama's cross-coupling of aryl fluorosilanes with aryl iodides.<sup>91</sup>

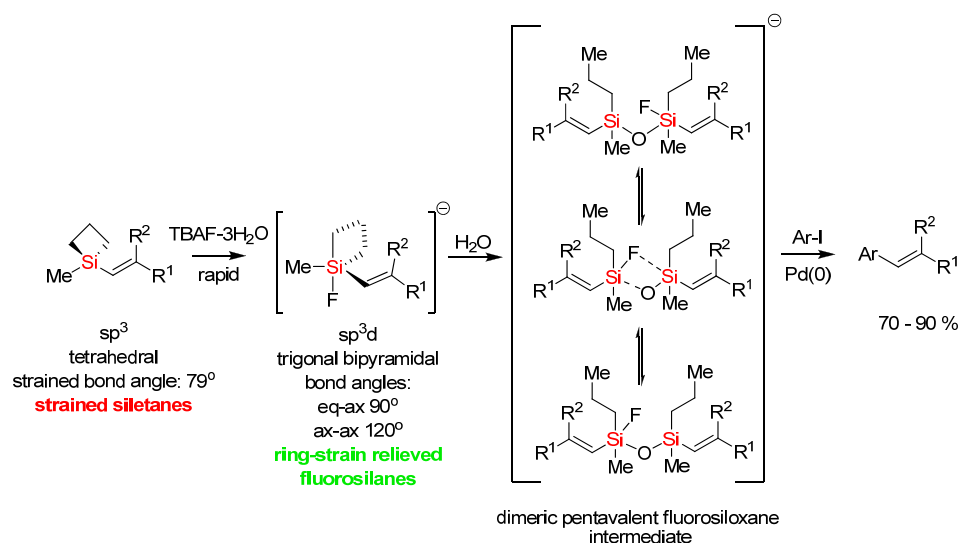
Aryl-aryl coupling reactions employing dichlorosilane derivatives were also achieved by Hiyama. The performance of ArSiCl<sub>2</sub>Et compounds is in fact superior to that of their ArSiF<sub>2</sub>Et analogues in coupling with a variety of aryl iodides for the preparation of highly functionalised biaryls as extremely low Pd catalyst loading levels are required (0.5 mol% *cf.* 5 mol% whilst employing ArSiF<sub>2</sub>Et as substrates).<sup>92</sup>

In 1997, Shibata reported a protocol for aryl-aryl cross-coupling by employing aryl trimethoxysilanes which were prepared by nucleophilic addition of aryllithium or aryl Grignard reagents to tetrachlorosilane followed by solvolysis with MeOH. Upon pre-treatment of the aryl trimethoxysilanes with TBAF, activated pentavalent aryl fluorotrimethoxysilicates were generated which participated in cross-coupling with a variety of aryl bromides catalysed by a catalytic amount of Pd(OAc)<sub>2</sub> with PPh<sub>3</sub> as a ligand. Electron deficient, neutral and rich aryl trimethoxysilanes coupled smoothly with aryl bromides bearing diverse functionalities to give biaryls in good yields. It is noteworthy that no homo-coupling products were detected and the other side-products were found in very limited amounts (Scheme 2.2.5).<sup>93</sup>



**Scheme 2.2.5.** Shibata's cross-coupling aryl trimethoxysilanes with aryl bromides facilitated by TBAF.<sup>93</sup>

In 1999, Denmark designed alkenylsilacyclobutanes (siletanes) as efficient coupling precursors for cross-coupling with activation by fluoride ions. The driving force for coupling was originally envisaged to accrue from released angle strain of the silacyclobutane moiety ( $79^\circ$  cf.  $109^\circ$  bond angle in the  $sp^3$  Si) during formation of the corresponding activated pentavalent fluorosilanes. However, it was subsequently found that these initial pentavalent fluorosilanes were transformed into dimeric fluorosiloxane intermediates, and these are in fact the active coupling intermediates (Scheme 2.2.6).<sup>92-94</sup>



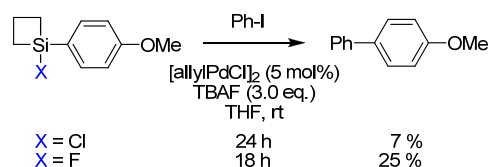
**Scheme 2.2.6.** Denmark's fluoride promoted silacyclobutane cross-coupling.<sup>94,95</sup>

Alkynyl- and alkenyl methylsilacyclobutanes are easily prepared and act as useful precursors of reactive intermediates for cross-coupling. Although aryl methylsilacyclobutanes might be envisaged to be coupled with aryl halides *via* similar dimeric fluorosiloxane intermediates, they proved to be too stable to be activated efficiently by fluoride ions and couple poorly.

Aryl siletanes bearing at least one heteroatom-substituent on Si are required to allow cross-coupling.<sup>96</sup> Even so, the reactivity of aryl siletanes is lower than alkenyl derivatives so harsher conditions are required to carry out cross-coupling reactions. Harsher conditions lead to undesired side-products such as those resulting from homo-coupling and protodesilylation, although the use of appropriate ligands can suppress these side-reactions.<sup>97</sup>

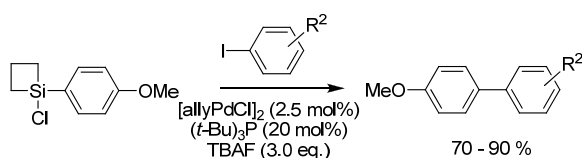
Denmark developed 4-anisyl halosilacyclobutanes to study the reactivity of this type

of aryl-aryl cross-coupling. Preliminary results revealed that coupling of 4-anisyl chlorosilacyclobutane with iodobenzene was promoted by TBAF to give the desired biaryl in just 7 % yield, whereas the more electronegative fluoride substituted congener coupled in 25 % yield under the same conditions (Scheme 2.2.7).<sup>86</sup>



**Scheme 2.2.7.** Pd-catalysed cross-coupling of (4-anisyl)halosilacyclobutanes with iodobenzene promoted by fluoride ions.<sup>86</sup>

Using optimised conditions, 4-anisyl chlorosilacyclobutane couples efficiently with electron-rich, neutral, -deficient heterocyclic and sterically hindered aryl iodides furnishing biaryls in excellent yields (Scheme 2.2.8).<sup>86</sup>

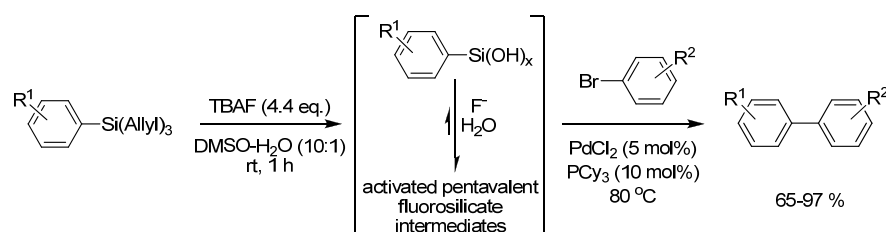


**Scheme 2.2.8.** Aryl-aryl cross-coupling of 4-anisyl chlorosilacyclobutane with functionalised aryl iodides.<sup>86</sup>

Aryl silanes such as halosilanes, trialkoxysilanes, silacyclobutanes (siletanes) and halosilacyclobutanes have been demonstrated to successfully serve as practical substrates to achieve cross-coupling with organic halides catalysed by Pd(0) and promoted by a source of nucleophile to form a pentavalent reactive intermediate. In order to constitute practical aryl-aryl cross-coupling reactions, at least one heteroatom on the arylsilane is essential. However, the drawback and limitation of these arylsilane surrogates is that they are labile to moisture, acidic and basic conditions, and unable to be purified by column chromatography. Recently, all-carbon-substituted alkenyl silanes (*e.g.* alkenyl 2-pyridyl-<sup>98</sup> and alkenyl 2-thienyl silanes)<sup>99</sup> have been developed as coupling partners, in which the heterocyclic-substituents on the Si act as precursors to hydroxyl groups after treatment with a source of fluoride ions. The corresponding alkenyl silanols are therefore formed *in situ* as the active intermediates for coupling. The improved stability of all-carbon-substituted alkenyl silanes overcomes the drawbacks and

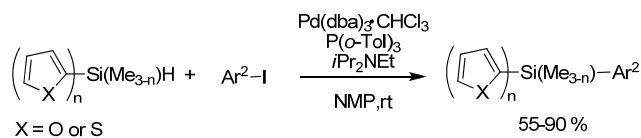
limitations encountered when using heteroatom-substituted silanes as coupling partners directly. The coupling processes are referred to as ‘safety-catch’ silanes.

In 2003, Hiyama discovered that allyl groups on silanes are converted into hydroxyl groups upon activation by fluoride ions. Aryl triallylsilanes were shown to be stable for a long periods of time to treatment with 1 M NaOH<sub>(aq.)</sub> and briefly stable while subjected to 1 M HCl<sub>(aq.)</sub>. However, treatment with TBAF in DMSO-H<sub>2</sub>O (10:1) furnished aryl silanol analogues which coupled with similar efficiencies as aryl silanes. Pentavalent fluorosilicate intermediates formed *in situ* were suggested to be the active species for effective coupling.<sup>100</sup> This protocol is compatible with aryl bromides bearing various electronic and steric demands and gives the desired biaryls in excellent yields (Scheme 2.2.9).<sup>101</sup>



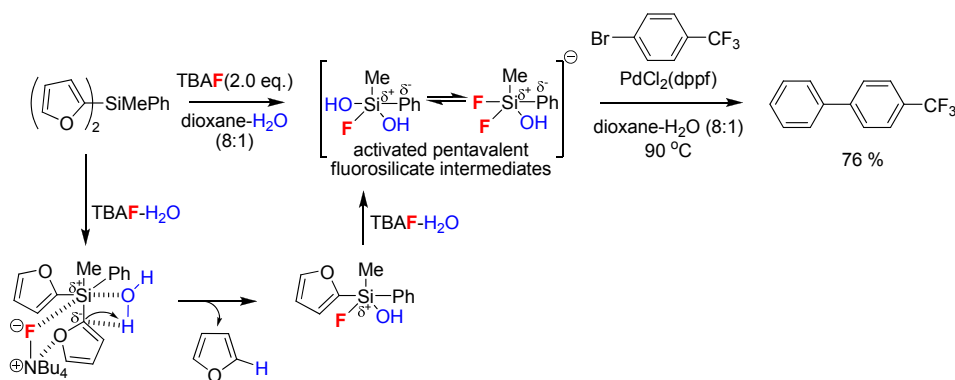
**Scheme 2.2.9.** Hiyama’s use of aryl triallylsilanes as surrogates for silanols for cross-coupling with aryl bromides facilitated by TBAF.<sup>101</sup>

In 2006, Murata reported a series of silylation reactions between (2-furyl)- and (2-thienyl)methylhydrosilanes and aryl iodides catalysed by Pd(0) to afford the corresponding aryl silanes. These silanes were suggested to be stable towards many chemical manipulations and serve as effective precursors to aryl silanols for cross-coupling reactions. This protocol provides a convenient and efficient method for the preparation of stable all-carbon-substituted silane-based coupling agents. For example, treatment of di(2-furyl)methylhydrosilane with iodobenzene in the presence of  $Pd(dba)_3 \cdot CHCl_3$  and  $tri(2-Tol)_3P$  gave phenyl di(2-furyl)methylsilane in 82 % yield. (Scheme 2.2.10).<sup>102</sup>



**Scheme 2.2.10.** Murata's silylation of aryl iodides by cross-coupling with (2-furyl)- and (2-thienyl)methylhydrosilanes.<sup>102</sup>

Upon treatment of phenyl di(2-furyl)methylsilane with TBAF and H<sub>2</sub>O, the 2-furyl groups coordinate with TBAF through an ionic interaction and deliver fluoride ion onto the Si centre mediating cleavage of the furan and formation of a pentavalent fluorosilicate.<sup>103,104</sup> The *in situ* formed fluorosilicate intermediate then cross-couples with *e.g.* 1-bromo-4-(trifluoromethyl)benzene catalysed by PdCl<sub>2</sub>(dppf) to give the biaryl product in 76 % yield (Scheme 2.2.11).<sup>102</sup>



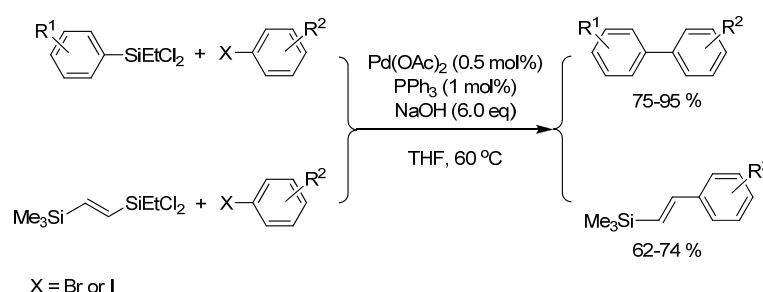
**Scheme 2.2.11.** Murata's cross-coupling of phenyldi(2-furyl)methylsilane and 1-bromo-4-trifluoromethylbenzene.<sup>102</sup>

## 2.2.2 Fluoride-free organosilane-based cross-coupling reactions

Although fluoride ion promoted Pd-catalysed organosilane-based cross-coupling protocols have shown some advantages and display high efficiency preparing biaryls, these methods are not applicable to substrates containing silyl protecting groups. In addition, fluoride ions are generally required in excess which presents difficulties for large-scale operation. Consequently, methods that do not require a fluoride activator are demanded.

In 1997, Hiyama first reported NaOH as a Lewis base activator to mediate cross-coupling of alkenyl- and aryl dichloroethylsilanes with aryl halides to give styrenes and biaryls at temperature lower than 60 °C with low catalyst loading (0.5 -

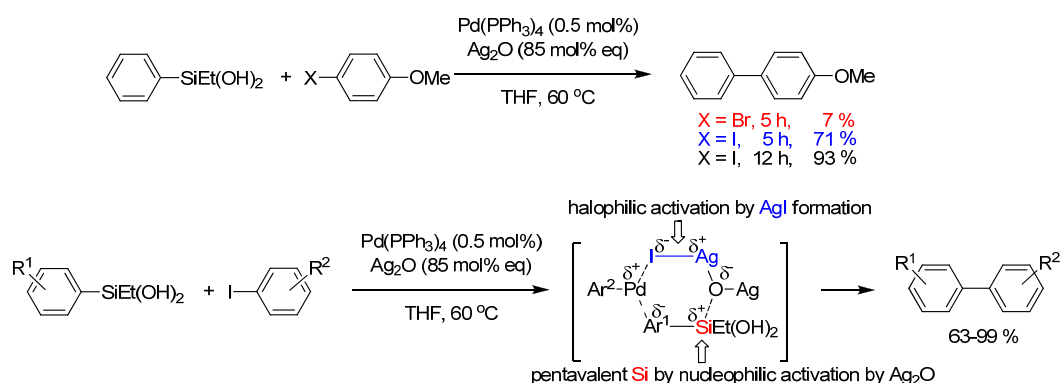
1 mol%). The KF-promoted cross coupling protocol required harsher conditions (*i.e.* 80-120 °C) and high Pd loading level (5 mol%),<sup>92</sup> for example, cross-coupling of 4-anisyl dichloroethylsilane with 2-bromopyridine in the presence of NaOH and catalytic amount of Pd(0) in THF at 60 °C gave the corresponding biaryl in 64 % yield whereas, KF promoted coupling reaction with the same halide using the difluoroethylsilane congener under catalytic conditions in DMF at 120 °C produced the biaryl in just 23 % yield. Moreover, silyl protection groups were tolerated under the coupling promoted by NaOH. In the case of coupling trimethylsilyl (TMS) protected alkenylchloroethylsilanes with aryl bromides, 2-TMS-styrenes were obtained in good yields (Scheme 2.2.12).<sup>105</sup>



**Scheme 2.2.12.** Hiyama's cross-coupling of aryl- and alkenyl dichloroethylsilanes with aryl halides promoted by NaOH.<sup>105</sup>

Hiyama also investigated cross-coupling of aryl silanols<sup>106</sup> and silanediols<sup>100</sup> with aryl halides activated by Ag<sub>2</sub>O. Aryl silanediols proved more reactive than the corresponding silanols which required longer reaction times and gave only moderate yields. By contrast, Ag<sub>2</sub>O promoted cross-coupling of silanediols derivatives with aryl iodides gave high yields. Furthermore, it is noteworthy that only a substoichiometric amount of Ag<sub>2</sub>O was required in contrast with large excess of NaOH required (85 mol% *cf.* 6.0 eq.).

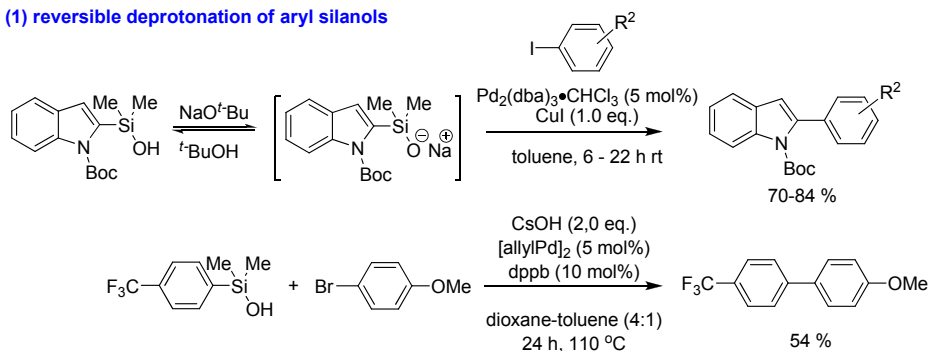
Hiyama suggested that the high affinity of silver salts for halides meant that Ag<sub>2</sub>O acts as a halophilic activator which interacts with the halides in the Ar<sup>2</sup>Pd<sup>II</sup>XL<sub>2</sub> complex, *via* a 6-membered transition state, polarising the Pd-halogen bond such that a cationic Pd-centre is formed. This might explain the superior coupling of aryl iodides relative to aryl bromides. Moreover, Ag<sub>2</sub>O may concomitantly coordinate to the silanediol rendering it pentavalent and therefore more reactive towards transmetalation (Scheme 2.2.13).<sup>100</sup>



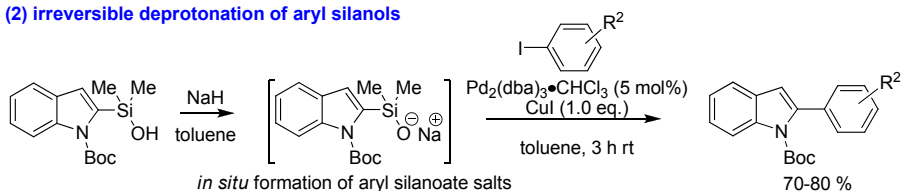
**Scheme 2.2.13.** Hiyama's cross-coupling of aryl silanediols with aryl iodides *via* a proposed reactive pentavalent intermediate formed by the bifunctional Ag<sub>2</sub>O activator.<sup>100</sup>

In 2008, Denmark developed a series of high performance fluoride-free cross-coupling reactions of alkenyl- and aryl dimethylsilanols (SiMe<sub>2</sub>OH) with organic halides under basic conditions. These methods employed various inexpensive Brønsted bases such as KOTMS, CsOH, NaO<sup>*t*</sup>Bu, NaH and NaHMDS as activators which form organosilanolate salts that promote the transmetalation step. Depending on the conditions, dimethylsilanoates are formed by reversible deprotonation, irreversible deprotonation, isolation, or *via* silanolate exchange (Scheme 2.2.14).<sup>107</sup>

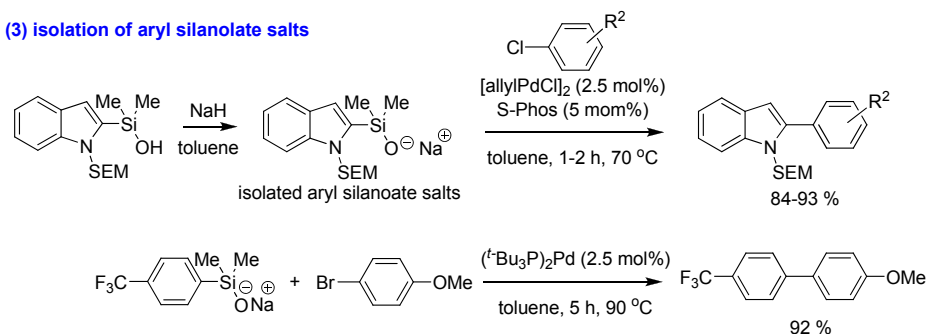
(1) reversible deprotonation of aryl silanols



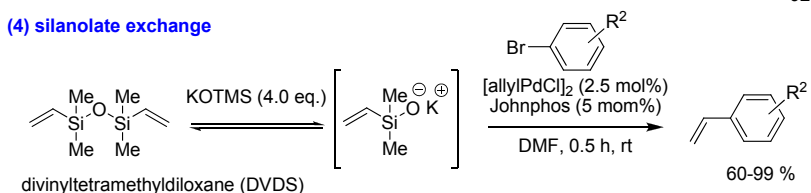
(2) irreversible deprotonation of aryl silanols



(3) isolation of aryl silanoate salts



(4) silanoate exchange

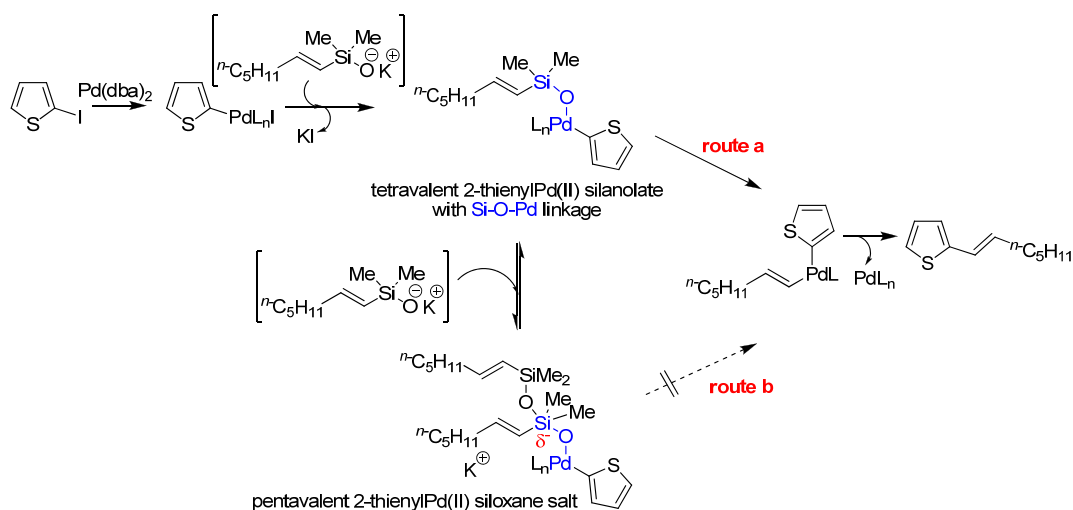


**Scheme 2.2.14.** Denmark's four methods for cross-coupling organosilanols with aryl halides promoted by Brønsted bases.<sup>107</sup>

Denmark performed experiments to elucidate mechanistic and kinetic features of these reactions. Based on examination of the turnover-limiting step in cross-coupling of 1-heptenyl dimethylsilanol with 2-iodothiophene, Denmark concluded that the major role of the organosilanoate salts was to accelerate the rate of transmetalation.<sup>108</sup>

Two possible transmetalation mechanisms were considered: route (a) where the transmetalation proceeded *via* the tetracoordinated 2-thienyl-Pd(II) silanoate intermediate, and route (b) where another molecule of deprotonated silanoate salt acts as a nucleophile attacking the tetracoordinated intermediate leading to a

pentavalent 2-thienyl-Pd(II) siloxane salt which facilitates an intramolecular transmetalation (Scheme 2.2.15).<sup>107</sup>



**Scheme 2.2.15.** Denmark's proposed mechanisms for silanolate transmetalation.<sup>107</sup>

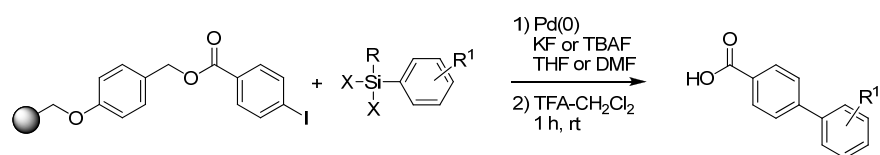
A first-order rate dependence on silanolate even when employing a stoichiometric amount of Pd(0) catalyst revealed that the transmetalation occurred directly through route (a). The proposed nucleophilic activation of the arylPd(II) silanolate intermediate by a second molecule of silanolate to form the pentavalent arylPd(II) siloxane salt (route b) would have displayed second-order dependence in silanolate.

The high reactivity of Brønsted base promoted silanol cross-coupling protocols appears therefore to be due to the formation of an arylPd(II) silanolate complex containing a Si-O-Pd linkage which undergoes rapid transmetalation. The structure of a complex containing a Si-O-Pd bond was elucidated by X-ray crystallography from an independently synthesised arylPd(II) aryl silanolate complex. Re-subjection of this isolated intermediate to the coupling conditions, without promoter, gave a quantitative yield of a biaryl.<sup>107</sup>

### 2.2.3 Phase-tagged organosilanes in cross-coupling reactions

No examples of phase-tagged organosilanes being used in synthesis have been reported but Hiyama has coupled soluble aryl difluoroalkylsilanes with solid-supported 4-iodobenzoic acid using TBAF as the promoter. TFA was used to effect traceless cleavage off the resin and the corresponding biaryl carboxylic acids were obtained in quantitative yield in the case of using aryl difluorocyclohexylsilanes

(Table 2.2.1).<sup>109,110</sup>



| Entry | R          | R <sup>1</sup> | X  | Yield (%)           |
|-------|------------|----------------|----|---------------------|
| 1     | Et         | 4-OMe          | F  | >99                 |
| 2     | cyclohexyl | 4-OMe          | F  | 98                  |
| 3     | Et         | 4-F            | F  | mixture of products |
| 4     | cyclohexyl | 4-F            | F  | 94                  |
| 5     | Et         | 2-OMe          | Cl | 82                  |
| 6     | cyclohexyl | 2-OMe          | F  | >99                 |

**Table 2.2.1.** Hiyama's cross-coupling of aryl halosilanes with solid-supported 4-iodobenzoic acid.<sup>109,110</sup>

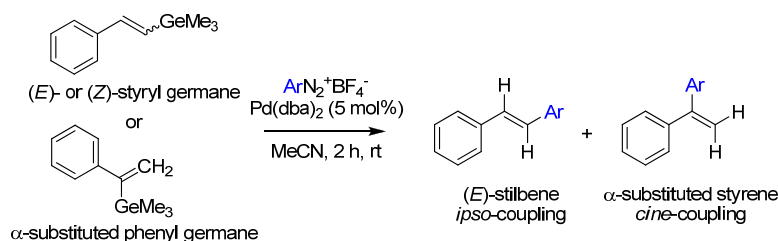
### 2.3 Pd-catalysed cross-coupling of organogermanes

Although in the same group as Si and Sn, Ge derivatives have been studied less extensively for cross-coupling. This is probably because of the higher cost and lower reactivity of organogermanes compared to organosilanes and organostannanes. Nevertheless, with several advantages over organosilanes and organostannanes, such as low-toxicity<sup>111-115</sup> and high tolerance to chemical manipulations, organogermanes deserve to be more widely used in organic synthesis.

Organogermanes exhibit better stability towards strongly nucleophilic and basic conditions because C-Ge bonds are less polarised than C-Si and C-Sn bonds. This is because Ge is the closest in electronegativity to C amongst the group 14 elements (C, 2.55; Si, 1.90; Ge, 2.01; Sn, 1.96 on the Pauling scale).<sup>114</sup> Although Ge is located a row below Si in the periodic table, it is more electronegative as a result of d-block contraction (also known as scandide contraction) in which the filled 3d electrons cannot shield efficiently the increasing nuclear charge for those elements which are positioned immediately after the first row of transition metals. This results in Ge having a small atomic radius and a relatively high electronegativity.<sup>116</sup> As a result, strong activation of organogermanes is required to achieve Ge hypervalency which is

probably essential for cross-coupling. Nevertheless, the less polarised C-Ge bond as compared to C-Sn and C-Si bonds provides a broader stability profile and allows for a wider range of chemical transformations prior to cross-coupling.

In 1990, Kikukawa published the first Pd-catalysed cross-coupling of alkenyl trimethylgermanes with arenediazonium tetrafluoroborates ( $\text{ArN}_2^+\text{BF}_4^-$ ) to give coupling products in good yields. However, the stereo- and regiochemistry of the products did not transfer cleanly from the configuration of the germane substrates (Table 2.3.1).<sup>117</sup>

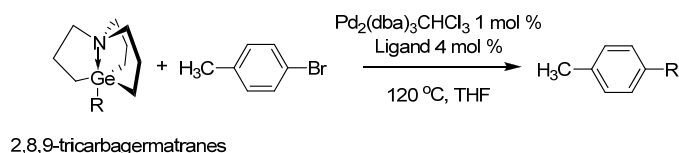


| Entry | Germanes<br>(E)- : (Z)- : $\alpha$ - | $\text{ArN}_2\text{BF}_4$                 | Yield<br>(%) | Product ratio<br>(E)- : $\alpha$ -sub. |
|-------|--------------------------------------|-------------------------------------------|--------------|----------------------------------------|
| 1     | 94 : 6 : 0                           | 4-Me- $\text{C}_6\text{H}_4$              | 82           | 52 : 48                                |
| 2     | 94 : 6 : 0                           | Ph                                        | 83           | 66 : 34                                |
| 3     | 94 : 6 : 0                           | 4- $\text{NO}_2$ - $\text{C}_6\text{H}_4$ | 81           | 85 : 15                                |
| 4     | 18 : 82 : 0                          | 4-Me- $\text{C}_6\text{H}_4$              | 85           | 64 : 36                                |
| 5     | 18 : 82 : 0                          | Ph                                        | 88           | 73 : 27                                |
| 6     | 18 : 82 : 0                          | 4- $\text{NO}_2$ - $\text{C}_6\text{H}_4$ | 95           | 88 : 12                                |
| 7     | 0 : 0 : 100                          | 4-Me- $\text{C}_6\text{H}_4$              | 85           | 100 : 0                                |
| 8     | 0 : 0 : 100                          | Ph                                        | 92           | 100 : 0                                |
| 9     | 0 : 0 : 100                          | 4- $\text{NO}_2$ - $\text{C}_6\text{H}_4$ | 88           | 100 : 0                                |

**Table 2.3.1.** Kikukawa's cross-coupling of styrenyl germanes with arenediazonium tetrafluoroborates.<sup>117</sup>

Cross-coupling of (E)- or (Z)-styrenyl trimethylgermanes with various arenediazonium salts gave a significant amount of  $\alpha$ -substituted styrenes *via* a *cine*-coupling pathway. Notably, regardless of the stereochemistry of the styrenyl germanes, (E)-stilbenes were obtained as the major *ipso*-coupling products (entries 1-6). The  $\alpha$ -substituted styrenyl germane exhibit noteworthy regio- and stereoselectivity to furnish (E)-stilbenes exclusively in good yields (entries 7-9).

Kosugi described the first arylgermane-based cross-coupling reactions in 1996. He cross-coupled a series of aryl-, alkenyl-, alkynyl- and allyl-2,8,9-tricarbagermatranes with 4-bromotoluene in the presence of  $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$  as catalyst with various phosphine ligands to give biaryls (Table 2.3.2).<sup>118</sup>



| Entry | R                  | Ligand                       | Yield (%)            |
|-------|--------------------|------------------------------|----------------------|
| 1     | <sup>n</sup> Butyl | $\text{PPh}(\text{2-Tol})_2$ | 8                    |
| 2     | Allyl              | $\text{PPh}_3$               | 88 (77) <sup>a</sup> |
| 3     | Phenyl             | $(\text{2-Tol})_3\text{P}$   | 95 (85) <sup>a</sup> |
| 4     | Vinyl              | $(\text{2-Tol})_3\text{P}$   | 82                   |
| 5     | 1-Ethoxyvinyl      | $\text{PPh}(\text{2-Tol})_2$ | 59                   |
| 6     | Phenylethynyl      | $\text{PPh}(\text{2-Tol})_2$ | 67                   |

<sup>a</sup> Isolated yields

**Table 2.3.2.** Kosugi's cross-coupling of 2,8,9-tricarbagermatranes and 4-bromotoluene.<sup>118</sup>

These cross-coupling reactions gave moderate to excellent yields except in the case where R was butyl (entry 1). Notably the reactions proceeded in the absence of fluoride ions due to the trans-annular coordination between the N and Ge which enhances the reactivity of the tricarbagermatranes by rendering the Ge centre permanently hypervalent.

In 2002, Oshima reported a convenient method for Pd-catalysed germylation of aryl iodides by tri(2-furyl)germane giving the corresponding arylgermanes for use as cross-coupling partners (Table 2.3.3).<sup>119</sup>

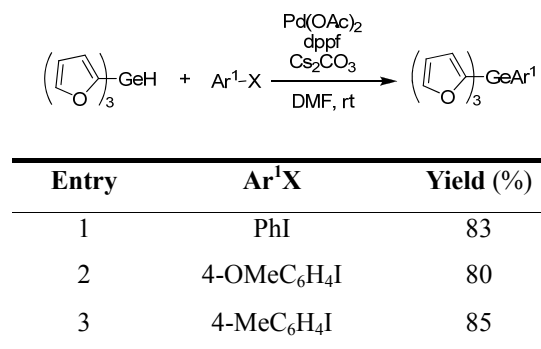


**Table 2.3.3.** Oshima's Pd-catalysed germylation of aryl halides with tri(2-furyl)germane.<sup>119</sup>

The coupling proceeded well with aryl iodides but was sensitive to sterically demanding and aryl bromide substrates which gave inferior yields (entries 4-6). The 2-furyl groups act as precursors to hydroxy groups in a similar manner to the 2-heteroarylsilane cases discussed previously.<sup>103,104</sup> After refluxing the aryl tri(2-furyl)germanes with TBAF in THF for 5 h, <sup>1</sup>H and <sup>19</sup>F NMR spectra indicated that the three furyl-substituents had been replaced by hydroxyl and fluoride groups leading to [ArGe(OH)<sub>3</sub>F]<sup>−</sup> as reactive intermediates for cross-coupling with various aryl halides, catalysed by Pd<sub>2</sub>dba<sub>3</sub> and P(2-furyl)<sub>3</sub> as ligand to yield biaryls (Table 2.3.4).<sup>119</sup>

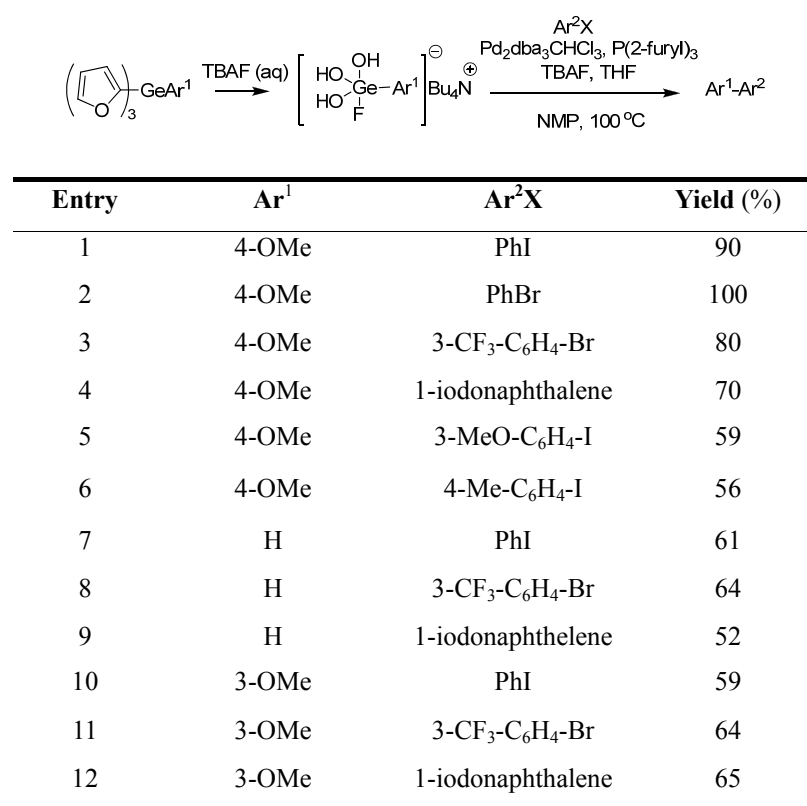


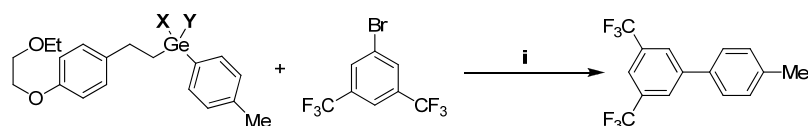
**Table 2.3.4.** Oshima's cross-coupling of tri(2-furyl)arylgermanes **94** and aryl halides.<sup>119</sup>

Both iodobenzene and bromobenzene gave excellent yields (entries 1 and 2). Aryl halides bearing electron-withdrawing groups gave higher yields than electron-donating groups (*cf.* entries 3, 5 and 6). Steric effects were also significant: 3-anisylsubstituted arylgermane afforded lower yields of biaryls than its 4-anisyl analogue (*cf.* entries 2 *vs.* 4 and 10 *vs.* 12).

No examples of phase-tagged organogermanes being used in synthesis had been reported prior to the work described in this thesis.

## 2.4 Preliminary Results – Prior work in the group

The germyl-Stille cross-coupling reaction has been developed in our group first by Chris Gripton (Spivey group, 1999-2004)<sup>120</sup> and then by Joseph Hannah (Spivey group, 2002-2006).<sup>121</sup> Gripton found that aryl dihaloalkylgermanes but not aryl monohaloalkylgermanes or trialkylgermanes cross-coupled with bis(3,5-trifluoromethyl)bromobenzene in the presence of Pd<sub>2</sub>dba<sub>3</sub> and PPh<sub>3</sub> to give the corresponding biphenyl in 36 % yield (Table 2.4.1).<sup>120,122</sup>



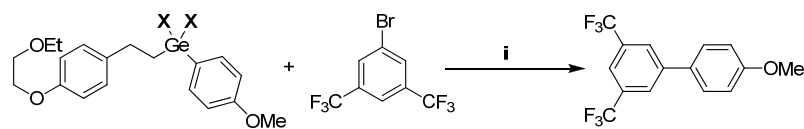
Reagents and conditions: i) Pd<sub>2</sub>dba<sub>3</sub>, PPh<sub>3</sub>, CsF, THF, reflux, 24 h.

| Entry | X  | Y  | Yield (%) <sup>a</sup> |
|-------|----|----|------------------------|
| 1     | Me | Me | 0                      |
| 2     | Me | Cl | 0                      |
| 3     | Cl | Cl | 36                     |

<sup>a</sup>: GC/MS results

**Table 2.4.1.** Gripton's demonstration of the effect of halogen substituents at germanium on cross-coupling.<sup>120,122</sup>

Hannah found that the dihydroxy germane generated *in situ* by treating a related dichloroalkylarylgermane with aqueous Na<sub>2</sub>CO<sub>3</sub> also coupled with bis(3,5-trifluoromethyl)bromobenzene under Gripton's conditions to give biphenyl in 35 % yield. Additionally, he found that treatment of the dichloroalkylarylgermane with copper(II) fluoride gave a 1:1 mixture of difluoroalkylarylgermane and dichloroalkylarylgermane, which cross-coupled in 45 % yield (Table 2.4.2).<sup>121</sup>



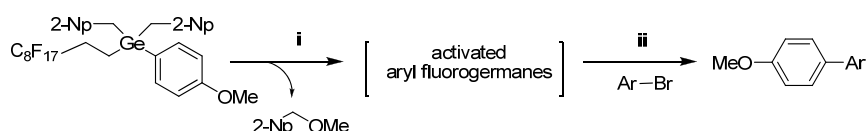
Reagents and conditions: i)  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol %), dppp (15 mol%), KF, DMF, 120 °C, 16 h.

| Entry | X                 | Yield (%) |
|-------|-------------------|-----------|
| 1     | OH                | 35        |
| 2     | F/Cl <sup>a</sup> | 45        |

<sup>a</sup>: 1:1 mixture of dichloro- and difluorogermane

**Table 2.4.2.** Hannah's use of dihydroxy and difluoro germanes for cross-coupling.<sup>121</sup>

These results suggested that more electronegative atoms at Ge give higher yields of cross-coupling products. Consequently, a photooxidation process was developed to access difluorogermanes. Light fluorous-tagged (*R<sub>f</sub>*-tagged) arylgermane was found to be 'activated' by irradiation with a high pressure Hg lamp in the presence of copper(II) tetrafluoroborate to give a presumed difluoroalkylarylgermane intermediate with liberation of two equivalents of 2-(methoxymethyl)naphthalene. Cross-coupling of this crude reaction mixture with three aryl bromides gave biaryl products in two cases (Table 2.4.3).<sup>121</sup>



Reagents and conditions: i)  $\text{Cu}(\text{BF}_4)_2$  (4 eq.), Pyrex tube, argon purged,  $h\nu$ ,  $\text{MeOH} : \text{MeCN} = 1:3$ , 1 h;  
ii)  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%), dppp (15 mol%), KF, DMF, 120 °C, 16 h.

| Entry | Ar                                           | Yield (%) <sup>a</sup> |
|-------|----------------------------------------------|------------------------|
| 1     | 3,5- $(\text{CF}_3)_2\text{C}_6\text{H}_3$ - | 42                     |
| 2     | 1-naphthyl                                   | 15                     |
| 3     | 4-BnOC <sub>6</sub> H <sub>4</sub> -         | -                      |

**Table 2.4.3.** Hannah's photolysis/cross-coupling of *R<sub>f</sub>*-tagged arylgermane.<sup>121</sup>

The overall yields of the photolysis/cross-coupling reactions were however lower than those using the isolated dichloroalkylarylgermanes as substrates. Nevertheless, these preliminary results provided proof-of-principle for the sequential photoactivation/cross-coupling strategy using trialkylarylgermanes as substrates.

## 2.5 Aims and objectives

The overall aim of the project was to develop the photoactivation/cross-coupling reaction of the *Rf*-tagged trialkylarylgermanes with aryl bromides into a powerful method for the synthesis of biaryls. In particular, the yields needed to be optimised, the scope and limitations delineated, the utilisation of the *Rf*-tag for rapid purification explored and the stability of the arylgermane precursors needed to be demonstrated. Additionally, application of the method in target synthesis was envisaged to highlight the above features.

Towards these ends, the following specific objectives for the project were identified:

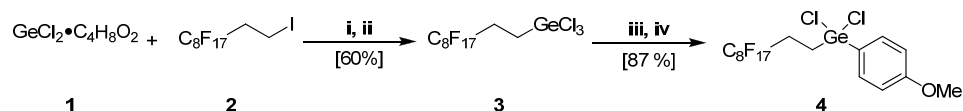
- 1) To prepare an *Rf*-tagged arylgermane as a model compound for optimisation of the efficiency of both the photoactivation and cross-coupling processes.
- 2) To identify the intermediate yielded by the photolysis of this model germane so as to aid optimisation of the subsequent coupling reactions.
- 3) To delineate the scope of the cross-coupling method by using various *Rf*-tagged arylgermanes as substrates for biaryl formation with a range of aryl halides under the optimised conditions.
- 4) To evaluate the stability profile of an *Rf*-tagged arylgermane compound under various reaction conditions.
- 5) To apply the method to the synthesis of a bioactive target compound. It was envisaged that carrying an arylgermane through a number of steps prior to coupling would underscore the chemical stability of these derivatives.

Progress towards these objectives is described in the following sections.

## 2.6 Results and Discussion

The first priority was to optimise the method for performing the cross-coupling reactions. Re-synthesis of Rf-tagged trialkylgermane **6a**, as used by Hannah, was required for this purpose.

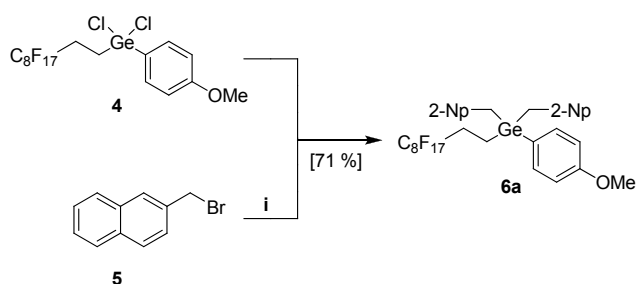
Rf-tagged trichlorogermane **3** was therefore prepared in 60 % yield by treatment of germanium(II) chloride · 1,4-dioxane complex **1** with fluoros-tagged iodide **2**. Insertion of dichlorogermylene liberated from this complex into the carbon-iodine bond occurs smoothly simply upon heating. The trichlorogermane **3** was then treated with 4-methoxyphenylmagnesium bromide in THF to give the tri(4-anisyl)germane intermediate which was dissolved in conc. HCl to effect cleavage of two molecules of anisole and give 4-anisyl dichlorogermane **4** in 87 % yield (Scheme 2.6.1).



**Scheme 2.6.1.** The synthesis of dichlorogermane **4**.

*Reagents and conditions:* i) sealed tube, 150 °C, 16 h; ii) conc. HCl, rt, 16 h; iii) 4-methoxyphenylmagnesium bromide 0.5 M in THF, reflux, 4 h; iv) conc. HCl, RT, 16 h.

4-Anisyl dichlorogermane **4** was then treated with 2-naphthymethyl Grignard reagent, which was generated *in situ* from 2-bromomethylnaphthalene **5**, and stirred for 2 h at room temperature to obtain Rf-tagged 4-anisyl germane **6a** in 71 % yield (Scheme 2.6.2).



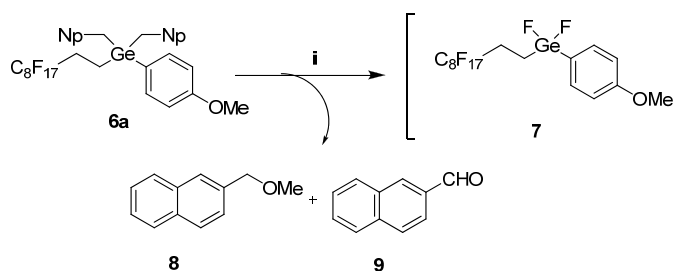
**Scheme 2.6.2.** Synthesis of the Rf-tagged arylgermane **6a**.

*Reagents and conditions:* i) Mg, THF, RT, 2 h.

The Rf-tagged 4-anisyl germane **6a** could be stored indefinitely and was employed as a model compound to investigate the photolysis reaction and also as a stock precursor for the preparation of other arylgermanes (*vide infra*).

### 2.6.1 Mechanism of photoactivation of Rf-tagged aryl germanes and structural elucidation of the reactive germane intermediates

The purpose of the two naphthylmethyl groups on the Ge is to function as all-carbon 'dummy' groups that can be oxidatively cleaved to provide two heteroatoms at the Ge centre. The 'activation' process which was developed by Hannah to achieve this transformation was *via* photolysis of arylgermane **6a** with a high pressure Hg lamp in the presence of  $\text{Cu}(\text{BF}_4)_2$ . In order to improve the efficiency of the sequential activation-cross coupling protocol and elucidate the structure of the proposed reactive intermediate which was tentatively assigned as difluorogermane **7**, the 4-anisyl germane **6a** was subjected to photolysis with 4 eq. of  $\text{Cu}(\text{BF}_4)_2$  in MeOH-MeCN (1:3). After irradiation with a high pressure Hg lamp for 1 h, the  $^1\text{H}$  NMR spectrum of the crude product revealed 2-(methoxymethyl)naphthalene **8**, a trace of 2-naphthaldehyde **9** and several signals assumed to be attributable to the expected difluorogermane **7** (Scheme 2.6.3).



**Scheme 2.6.3.** Photolysis of fluorine-tagged arylgermane **6a** – use of  $\text{Cu}(\text{BF}_4)_2$ .

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$  (4 eq.), Pyrex tube, argon purged, hv, MeOH : MeCN = 1:3, 1 h.

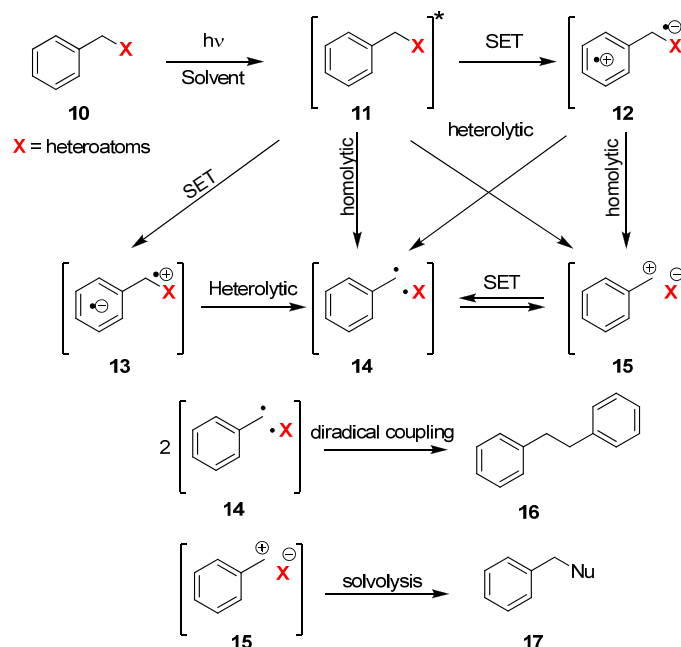
The high pressure Hg lamp provides an intense, wide band of emission from 200 to 600 nm (approximately 125 watts output). Unlike the output of a low pressure Hg lamp, the lines provided by this lamp are weak below 280 nm and the major lines are at 313, 365, 404, 435, 546 and 577 nm.<sup>123</sup> The most intense output is at 365 nm. In order to cut out shorter wavelengths and to avoid undesired reactions, a filter is needed. Our photolysis reactions were carried out in Pyrex tubes with a 1 mm wall thickness. For several conventional glass filters, the percentage of transmission is listed in Table 2.6.1.<sup>124</sup>

| Filters | The percentage of transmission |          |        |
|---------|--------------------------------|----------|--------|
|         | 20%                            | 50%      | 90%    |
| Quartz  | < 200 nm                       | < 200 nm | 240 nm |
| Vycor   | 200 nm                         | 220 nm   | 280 nm |
| Corex   | 270 nm                         | 290 nm   | 360 nm |
| Pyrex   | 290 nm                         | 300 nm   | 360 nm |

**Table 2.6.1.** The percentage of transmission for glass filters (1 mm thickness).<sup>124</sup>

It can be seen that the cut-off wavelength for a Pyrex tube is below 360 nm. Therefore, light impinging on the reaction solution in our experiments is predominately of 360 nm or above. The high energy far UV region is filtered out by the Pyrex flask. This minimises the possibility of unwanted photochemical reactions following absorption by the arylgermane moiety.

The photochemical process is initiated by photocleavage of one benzylic C-Ge bond. A mechanism for this process can be proposed based on the work of Fleming, who studied primarily the excited state photocleavage of benzylic C-S bonds (Scheme 2.6.4).<sup>125,126</sup>



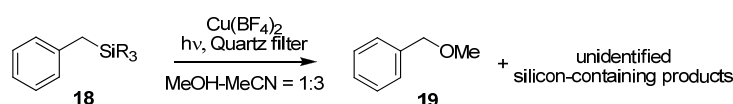
**Scheme 2.6.4.** Fleming's proposed mechanism of photocleavage of benzylic C-X bonds.<sup>125,126</sup>

Irradiation of compound **10** results in the formation of the excited state intermediate **11**. This can undergo either single electron transfer (SET) to form intermediates **12** or

**13** or undergo homolytic cleavage to form bi-radical intermediate **14**. The bi-benzyl product **16** is produced by radical coupling and is accompanied by the formation of other products *via* radical intermediates.

Based on this mechanism, there are three possible pathways for the formation of ion pair intermediate **15**: by heterolytic cleavage of excited state **11**, by homolytic cleavage of intermediate **12** or by SET from bi-radical **14**. Fleming found that electron-donating groups (EDGs) at the *meta*- position of the aryl ring of the ion pair intermediate **15** significantly enhanced solvolysis to give the final product **17**. This substituent effect was also reported by Zimmerman who analysed the excited states of benzylic compounds and concluded that the electron density of EDG-substituted aryl rings in the excited state are higher at the *meta*- than at the *para*-position.<sup>127</sup> Hence, *meta*-EDGs can tilt the equilibrium in favour of the photosolvolysis product **17**, this phenomenon is named as the *meta* effect.

A study of photodissociation for benzylic group 14 organometallic compounds in the presence of Cu(II) salts was published by Mizuno in 1988. Benzyltrialkylsilanes **18** were irradiated with a high pressure Hg lamp and Cu(BF<sub>4</sub>)<sub>2</sub> in MeOH-CH<sub>3</sub>CN (1 : 3) as solvent with a quartz filter (cut off < 200 nm) to afford methyl benzyl ether **19** accompanied by Cu(I) salts (Scheme 2.6.5).<sup>128</sup>

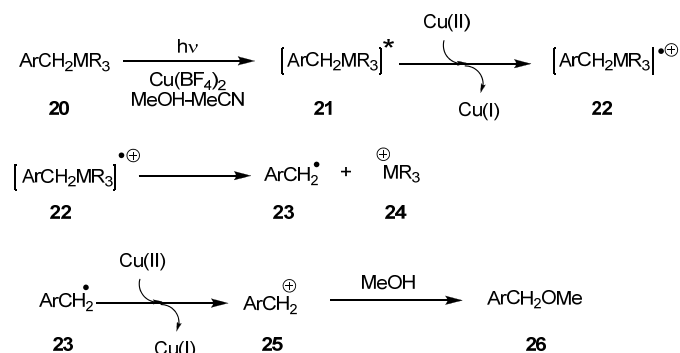


**Scheme 2.6.5.** Mizuno's photocleavage of benzyltrialkylsilanes.<sup>128</sup>

This is an alternative method to convert benzylsilanes into methyl ethers (and potentially to the corresponding alcohols) without the involvement of peroxide oxidants or the need for a phenyl silane as required for the Fleming-Tamao reaction.<sup>129</sup>

(Naphthylmethyl)trialkylsilanes and (phenanthrylmethyl)trialkylsilanes were also formed by Mizuno to undergo photosolvolysis reactions and for these substrates a Pyrex filter could be employed to give related methyl aryl ethers in excellent yields. The corresponding benzyltrialkylgermanes and benzyltrialkylstannanes were also studied. Their reactivity was found to follow the order: organostannanes > organogermanes > organosilanes. The following mechanism of solvolysis was

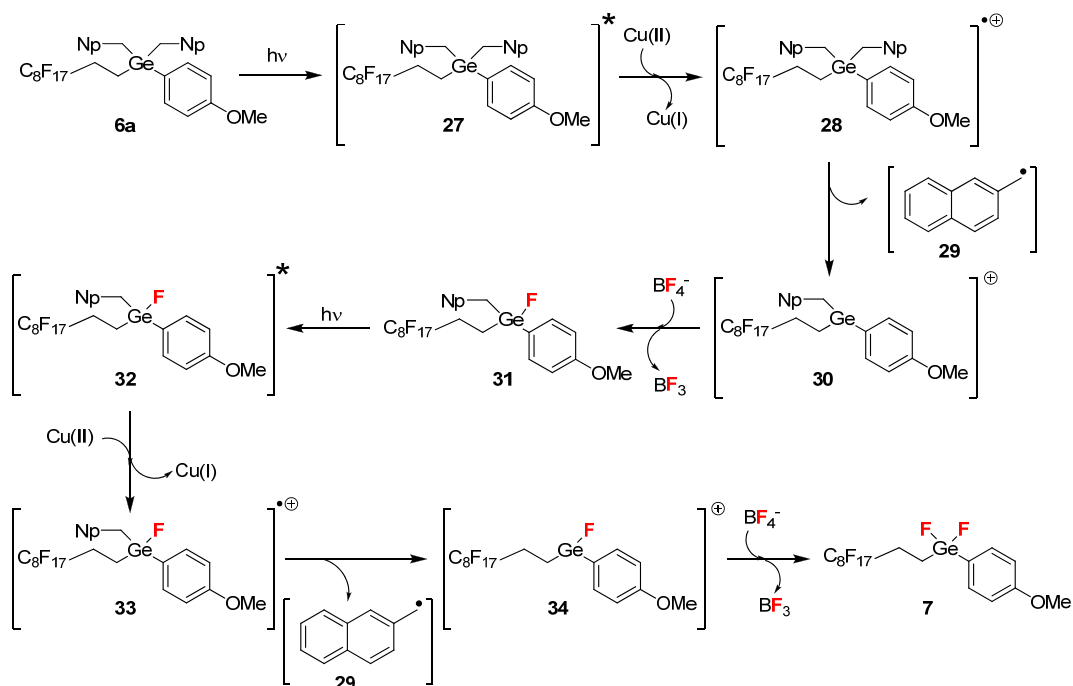
suggested (Scheme 2.6.6).<sup>128</sup>

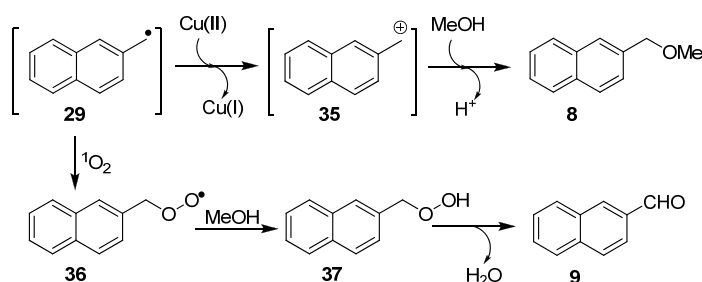


**Scheme 2.6.6.** Mizuno's mechanism for of benzyltrialkyl group 14 metal photosolvolysis reactions.<sup>128</sup>

Unlike Fleming, Mizuno suggested that excited state intermediate **21** undergoes homolytic cleavage or SET to form arylmethyl radical **23**, which is then oxidised by Cu(II) yielding the arylmethyl cation **25**. The photosolvolysis product, methoxy arylmethyl ether **26**, is formed by addition of methanol to arylmethyl cation **25**. The Cu(II) acts as an oxidant to trap an electron from the arylmethyl radical **23** and to force the reaction towards the formation of arylmethyl cation **25**.

By combining the ideas of Fleming and Mizuno, the following process of photolysis for the *R<sub>f</sub>*-tagged arylgermane **6a** can be proposed (Scheme 2.6.7).



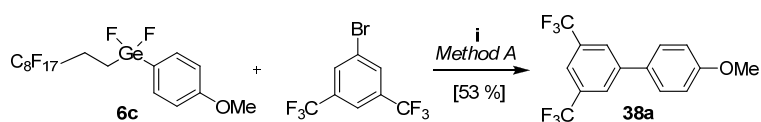


**Scheme 2.6.7.** Proposed mechanism for photolysis of R<sub>f</sub>-tagged arylgermane **6a**.

The radical cation **28** is formed from the excited state intermediate **27** through SET from the Cu(II) salt. Heterolytic cleavage then gives cation **30** and naphthylmethyl radical **29**. The germyl cation **30** is trapped by fluoride ion from the tetrafluoroborate to give the mono fluorinated arylgermane **31** which then undergoes the same process again to give the mono fluoro aryl germyl cation **34**. This reacts with tetrafluoroborate to give activated difluoro arylgermane **7**.

The naphthylmethyl radical **29** is either oxidised by Cu(II) to give a benzylic cation which reacts with MeOH to form 2-(methoxymethyl)naphthalene **8**, or reacts with singlet oxygen (<sup>1</sup>O<sub>2</sub>), produced by the action of UV light on dissolved oxygen in the solution, to give naphthylmethyl peroxide **37** which dehydrates to give 2-naphthaldehyde **9**. This latter pathway can be prevented by vigorous degassing with argon prior to UV irradiation. Nevertheless, the formation of singlet oxygen in the reaction mixture was found not to affect the efficiency of the overall photoactivation process or the subsequent cross-coupling reaction and was not performed routinely.

The crude product of the photolytic activation process (*i.e.* Scheme 2.6.3) containing the presumed difluoro arylgermane **7** was subjected to cross-coupling with 3,5-bis(trifluoromethyl)bromobenzene, catalysed by PdCl<sub>2</sub>(MeCN)<sub>2</sub> in DMF at 120 °C as described by Hannah<sup>121</sup> (*Method A*). Biphenyl **38a** was obtained in 53 % yield (Scheme 2.6.8).

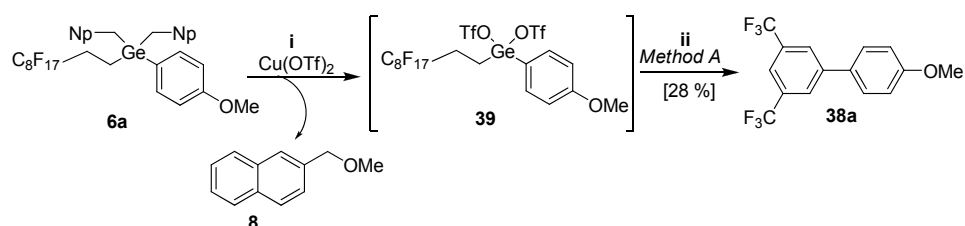


**Scheme 2.6.8.** Cross-coupling of difluoro fluororous-tagged arylgermane **6c** with 3,5-bis(trifluoromethyl)bromobenzene.

*Reagents and conditions:* i) *Method A*: PdCl<sub>2</sub>(MeCN)<sub>2</sub>, dppp, KF, DMF, 120 °C.

The photoactivation of fluororous-tagged arylgermane **6a** was also carried out using copper(II) triflate under the same conditions as described above to give a mixture tentatively assigned as the ditriflate **39** and 2-(methoxymethyl)naphthalene **8** (as identified by GC-MS). The formation of 2-(methoxymethyl)naphthalene **8** is a key indicator of success of the photoactivation process.

This crude ditriflate **39** was then cross-coupled with 3,5-bis(trifluoromethyl)bromobenzene as before to obtain biphenyl **38a** in 28 % yield (*Method A*) (Scheme 2.6.9).



**Scheme 2.6.9.** Photolysis of fluororous-tagged arylgermane **6a** – use of Cu(OTf)<sub>2</sub>.

*Reagents and conditions:* i) Cu(OTf)<sub>2</sub> (4 eq.), Pyrex tube, Argon, hv, MeOH : MeCN = 1:3, 1 h; ii) 3,5-bis-(trifluoromethyl) bromobanzen, *Method A*: PdCl<sub>2</sub>(MeCN)<sub>2</sub>, dppp, 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>Br, KF, DMF, 120 °C.

As this was an inferior yield to that obtained when using Cu(BF<sub>4</sub>)<sub>2</sub> as the activating agent, the latter was used in all subsequent reactions.

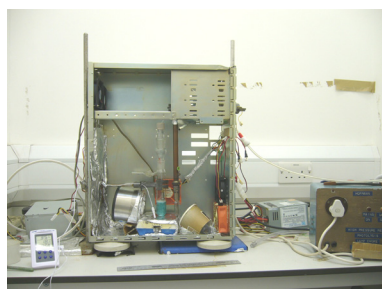
### 2.6.1.1 The photoreactor

The above photolysis reactions were carried out using a cardboard box as a reaction chamber with a gap of 30 cm between the Pyrex tube and a 125 Watt Cathodeon high pressure Hg vapour lamp (type HPK 125). A 30 cm light path was necessary to prevent over-heating of the reaction solution. This was the prototype photoreactor set-up as used by Hannah. Long periods of photolysis were not possible with this set-up as this caused extensive evaporation of solvent.

In order to enhance and optimise the efficiency of photolysis and to solve the over-heating, a photoreactor was constructed from an upright computer tower. Using this apparatus the temperature in the Pyrex tube is maintained below 35 °C after exposure to the UV lamp for over 2 h with a 6-cm light path. The short light path

enhances the UV intensity significantly which is beneficial for photolysis.

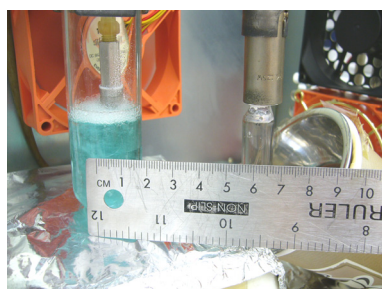
The main features of the photoreactor are: (a) five 12V rotary cooling fans are installed two of which are speed-adjustable (Figure 2.6.1a); (b) a set of concave reflectors focus the UV light on the Pyrex tube and a digital temperature sensor (Figure 2.6.1b); (c) a 6-cm light path is possible (Figure 2.6.1c) and (d) the reactor can be sealed so that all the UV light is contained within in the chamber (Figure 2.6.1d).



(a) an overview of the photoreactor



(b) a set of reflectors and digital thermosensor



(c) a 6-cm light path



(d) sealed reactor with outer shield.

**Figure 2.6.1.** Features of the Tseng photoreactor.

This photoreactor has enhanced photo-efficiency and cooling relative the set-up used by Hannah. Moreover, with the more powerful cooling system it is possible to maintain the photolysis at lower temperature than in the previous apparatus. This reduces the opportunity for undesired thermal pathways and pyrolysis of the activated arylgermane products. After the optimisation process described below, all photolysis reactions were performed in this photoreactor under optimised and normalised conditions.

### 2.6.1.2 Optimisation of photolysis efficiency and attempts to identity the reactive photolysis products

$^{19}\text{F}$  Nuclei are the second most sensitive nuclei for NMR spectroscopy after protons with a sensitivity of 0.83 relative to  $^1\text{H}$ . They also have spin quantum number  $+1/2$ . Consequently, we considered that  $^{19}\text{F}$  NMR would be a powerful tool to aid our understanding of the photochemical activation process and to help elucidate the structures of the germane intermediates.

According to the proposed mechanism of photolysis (*cf.* Scheme 2.6.7), this process is expected to proceed in a stepwise manner. This suggests that it should be possible to capture the mono-fluoronated arylgermane **31**. In order to address this point, Rf-tagged arylgermane **6a** was photolysed for a short period of time (15 min) and then the resulting crude product, following solvent evaporation, was submitted for both  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectroscopy. No starting arylgermane **6a** remained as judged by inspection of the  $^1\text{H}$  NMR spectrum but the major constituent still contained a 2-naphthylmethyl group. Analysis of the  $^{19}\text{F}$  NMR spectrum revealed a signal at  $\delta_{\text{F}}$  -203 ppm which was distinct from those peaks representing the perfluoroalkyl chain ( $\delta_{\text{F}}$  -80 ~ -125 ppm). The signal at  $\delta_{\text{F}}$  -203 ppm was assigned as corresponding to a germynyl monofluoride species. Moreover, the MS ( $\text{EI}^+$  mode) of this product displayed a peak at  $m/z = 788$ , as expected for the mono-fluoro arylgermane **31** (Scheme 2.6.7).

The  $^{19}\text{F}$  NMR of mono-fluoro germane **31** was not entirely pure and contained three low intensity but distinct signals located at  $\delta_{\text{F}}$  -162 ~ -165 ppm. It was considered that these might correspond to down-stream products of photolysis, such as the difluoro arylgermane **7**. To test this hypothesis, the mono-fluoro arylgermane **31** was resubjected into the photolysis conditions for another 30 min.  $^{19}\text{F}$  NMR of the crude mixture following this process clearly indicated that the intensity of the peak at  $\delta_{\text{F}}$  -203 ppm had decreased whilst the three peaks at around  $\delta_{\text{F}}$  -164 ppm had increased. Assuming that the growing peaks corresponded to the difluoro arylgermane, it was clear that the second photooxidation was a more sluggish process than the first (from arylgermane **6a** to mono-fluoro germane **31**). An additional 1 h of exposure to the UV light was sufficient to complete the conversion; the peak for the mono-fluoro germane at  $\delta_{\text{F}}$  -203 ppm had disappeared, whereas the three major signals at

$\delta_F$  -162.6, -163.0 and -164.3 ppm were strong with a minor set of peaks at  $\delta_F$  -162.0, -162.3 and -162.7 ppm also now apparent (Figure 2.6.2).

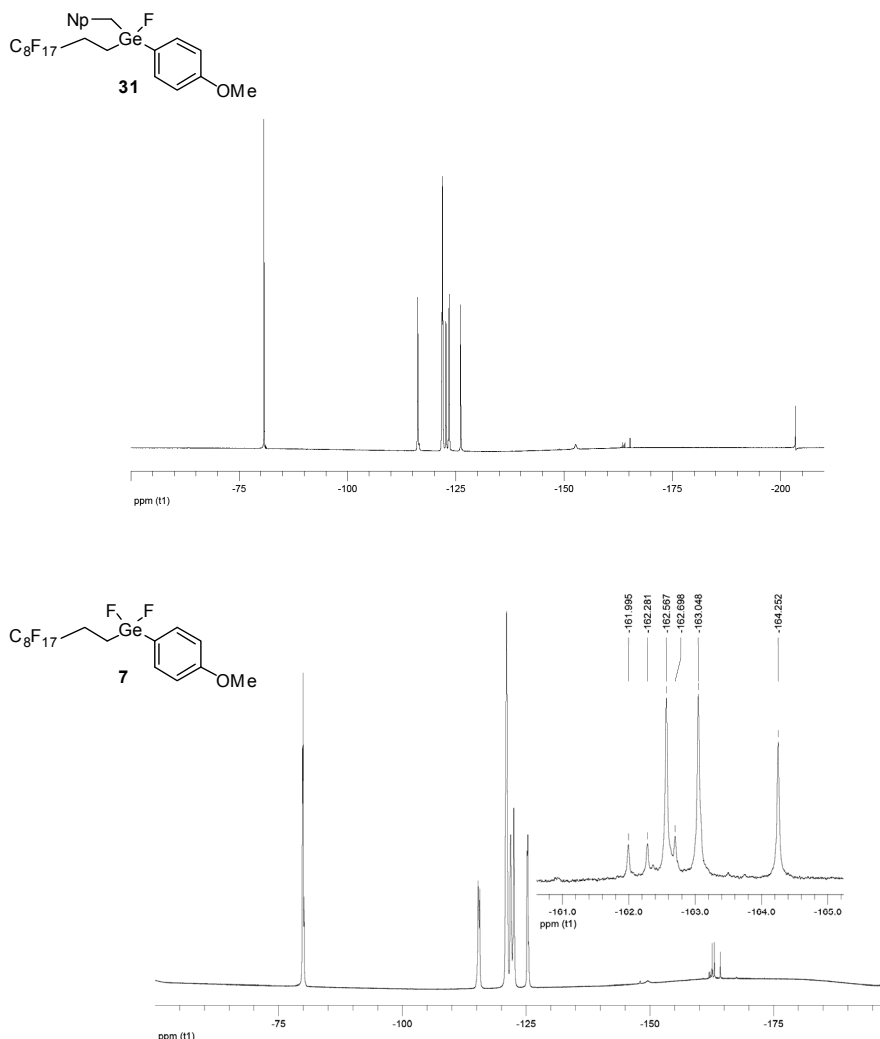


**Figure 2.6.2.**  $^{19}\text{F}$  NMR spectra of mono-fluoro germane **31** and 'di-fluoro germane' **7** with expansion at  $\delta_F$  -161 ~ -165 ppm for the latter.

The presence of three peaks in the  $^{19}\text{F}$  NMR spectrum of the 'difluoro germane' was an unexpected outcome and indicated the photoactivated arylgermane was not a single component. Extensive efforts were made to isolate and characterise these intermediates including the use of F-SPE and crystallisation techniques. Unfortunately, none of these were successful. The mixture was inseparable and so our attention turned to using  $^{19}\text{F}$  NMR to characterise the mixture.

In view of their inseparability and constant relative integration two possibilities were considered: i) these three peaks were on three different germane species; or ii) the two downfield peaks (at  $\delta_F$  -162.6 and -163.0 ppm) were from one molecule and the

further upfield peak (at  $\delta_F$  -164.3 ppm) was from another component in equilibrium with the other. In order to address this,  $^{19}\text{F}$  NMR spectra of the mixture were recorded on two spectrometers operating at different field strengths. Superimposed NMR traces across the region of interest are shown below (Figure 2.6.3)

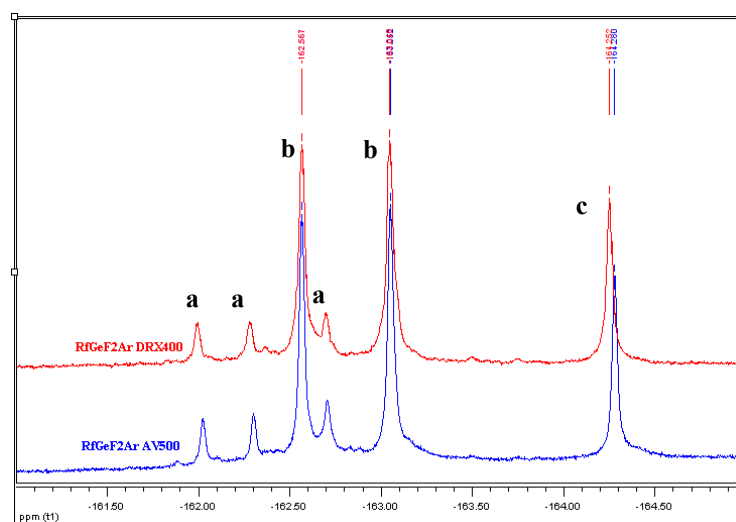


**Figure 2.6.3.**  $^{19}\text{F}$  NMR spectra of ‘di-fluoro germane’ **7** at 376.5 and 470.5 MHz (red and blue traces, respectively) in the region -162 ~ -165 ppm.

These  $^{19}\text{F}$  NMR spectra revealed that there are two major components assigned as compounds **b** and **c** and one minor compound **a** that co-exist in this mixture. The peaks for compound **b** superimposed perfectly as did the other three minor peaks corresponding to compound **a**. By contrast, the peak for compound **c** at  $\delta_F$  -164.3 ppm shifted its position indicating that this signal was from a separate species. Possible structures for these intermediates were proposed as a difluorogermane dimer which can exist in two isomeric forms **a** and **b** and a monomer **c**.

A Diffusion-Ordered Spectroscopy (DOSY) NMR experiment can resolve signals from different components in a mixture based on their different translational diffusion coefficients and has been employed to characterise reactive intermediates formed *in situ* during reactions.<sup>130</sup> The diffusion coefficient ( $D$ ) of a molecule is correlated to its size, shape, volume, molecular weight and tumbling speed. A large diffusion coefficient is characteristic of a high mobility, low molecular mass component.

In the event, the 2D  $^{19}\text{F}$  DOSY spectrum of the photolysis product solution clearly showed that compound **b** ( $D = 5.19 \times 10^{-10} \text{ m}^2/\text{s}$ ) and compound **c** ( $D = 7.79 \times 10^{-10}$

$\text{m}^2/\text{s}$ ) have similar diffusion coefficients which are larger than that of compound **a** ( $D = 4.10 \times 10^{-10}$ ). This is consistent with **a** and **b** corresponding to two dimeric forms of the difluorogermane and compound **a** being the monomer (Figure 2.6.4).

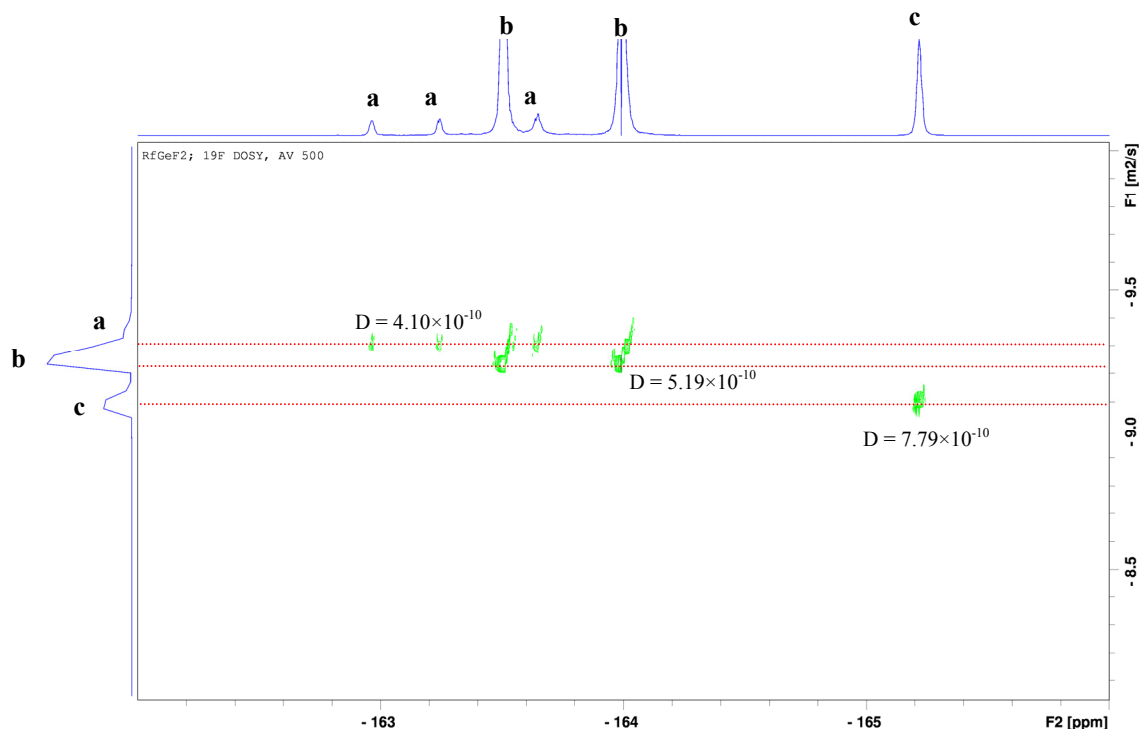
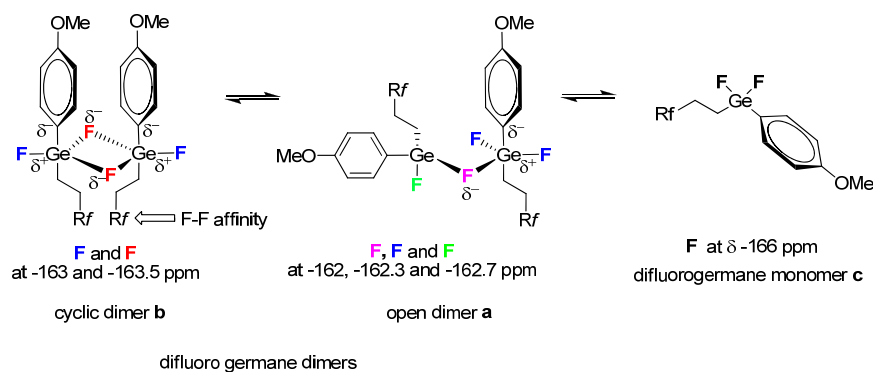


**Figure 2.6.4.**  $^{19}\text{F}$  DOSY spectrum of the mixture obtained from photolysis of arylgermane **6a**.

Although the diffusion coefficient is proportional to the molecular weight of a molecule, internal reference molecules are required to achieve accurate diffusion coefficient-molecular mass conversions by the Stokes-Einstein equation.<sup>131</sup>

The structures of the photolysis products were therefore proposed to be these shown below (Scheme 2.6.10).



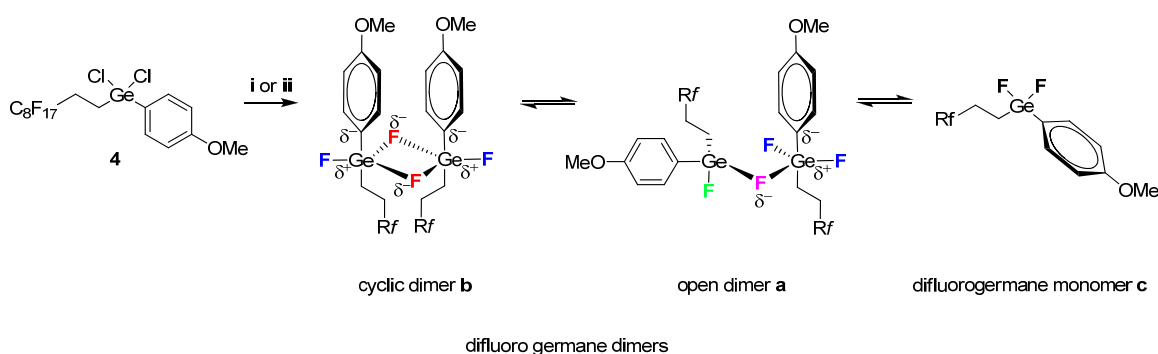
**Scheme 2.6.10.** Proposed structures of the dimers and monomer of the difluoro germane **7**.

The cyclic ‘head-to-head’ dimer **b** contains two magnetically inequivalent fluorine environments accounting for the two signals seen in the  $^{19}\text{F}$  NMR. This structure would be expected to benefit from attractive  $\pi$ - $\pi$  interactions between the aryl rings as well as attractive  $\text{F}\leftrightarrow\text{F}$  interactions between the fluorine tags. The corresponding ‘head-to-tail’ dimer would display a similar spectrum but is presumably not formed because these interactions are absent.

Organotin difluoride compounds are known to aggregate through double Sn-F-Sn bridges to form four-membered cyclic structures analogous to those proposed above.<sup>132,133</sup> However, organogermane compounds with two Ge-F-Ge bridges are, to the best of our knowledge, unknown.

The open dimer **a** is proposed to be in equilibrium with dimer **b**. This dimer contains one Ge-F-Ge bridge resulting in three chemically non-equivalent fluorine environments. Although ring-strain is released upon opening in the dimer **a**, the open dimer **a** is expected to be a minor component of equilibrating mixture because of a propensity to re-close to form cyclic dimer **b**.

To investigate the self-assembling and equilibrating behaviour of the difluorogermane, the preparation of this intermediate was undertaken by substitution of dichlorogermane **4** with two different sources of fluoride: AgF and AgBF<sub>4</sub>.<sup>134</sup> Both the resulting crude product mixtures were examined by  $^{19}\text{F}$  NMR spectroscopy. Both the spectra exhibited identical signal patterns as observed following the photolysis experiments (as described above). This provides strong evidence for the self-assembly of the equilibrating difluoro germane species (Scheme 2.6.11).



**Scheme 2.6.11.** Nucleophilic substitution of dichlorogermane **4** with AgF and AgBF<sub>4</sub>.  
*Reagents and conditions:* i) AgF, Et<sub>2</sub>O, rt, 16 h; ii) AgBF<sub>4</sub>, Et<sub>2</sub>O, rt, 16 h.

### 2.6.1.3 Conclusions

Photolytic activation of aryl bis(2-naphthymethyl)germanes has been carried out in a new photoreactor. This photoreactor was constructed from a PC case and provides enhanced photo-efficiency and cooling capacity *via* rotatory fans relative to the previous set-up. This avoids pyrolysis of the activated products.

The photocleavage of the first of the two 2-naphthymethyl substituents is complete within 15 ~ 20 min in the presence of 4 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub> in a mixed MeOH-MeCN solvent system. The mono-fluoro germane intermediate **31** was isolated and fully characterised.

Monitoring by <sup>19</sup>F NMR during subsequent photolysis revealed that the mono-fluoro germane intermediate is converted to the difluoro germane **7** more slowly (UV exposure time > 1 h). The mono-fluoro germane provides a single peak in the <sup>19</sup>F spectrum due to its Ge-F unit whereas the difluorogermane, unexpectedly, provides a more complex set of peaks in the region  $\delta_F$  -161 ~ -165 ppm.

1D and 2D <sup>19</sup>F NMR spectra of difluoro germane **7** revealed it to exist in solution as three components, proposed to be a monomer **c** a head-to-head cyclic dimer **b** and an open dimer **a**.

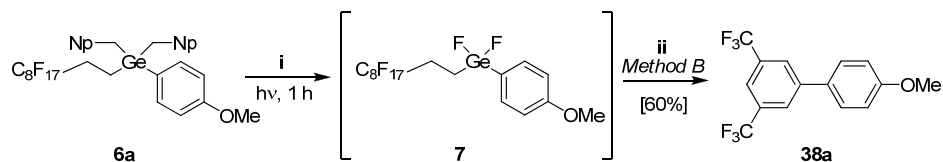
Independent preparation of difluoro germane **7** by substitution of dichlorogermane **4** in the presence of two different fluoride sources gave identical <sup>19</sup>F NMR spectra to those obtained from photolysis of aryl bis(2-naphthymethyl)germane.

Henceforward in this thesis the difluorogermane photolysis products will be depicted as monomer form **c** in schemes but the presence of an equilibrating mixture of species is implied.

## 2.6.2 Delineation of the scope and limitations of germyl-Stille cross-coupling reactions promoted by copper(I) iodide

### 2.6.2.1 Development of new conditions for germyl Stille coupling

Li *et al.* have reported that the efficiency of the Hiyama reaction can be improved by using bulky, electron-rich phosphine ligands such as tri-2-tolyl phosphine [P(2-Tol)<sub>3</sub>], TBAF as the nucleophilic promoter and PdCl<sub>2</sub>(MeCN)<sub>2</sub> as the catalyst.<sup>134</sup> Therefore, these conditions were applied to our germyl-Stille coupling reaction. Thus, following photolysis of arylgermane **6a** in the presence of Cu(BF<sub>4</sub>)<sub>2</sub> as usual, cross-coupling with 3,5-bis(trifluoromethyl)bromobenzene was performed using the new conditions. Biphenyl **38a** was obtained in 60 % yield (*Method B*; Scheme 2.6.12). This yield is higher than previously obtained (53 %, *cf.* Scheme 2.6.8).

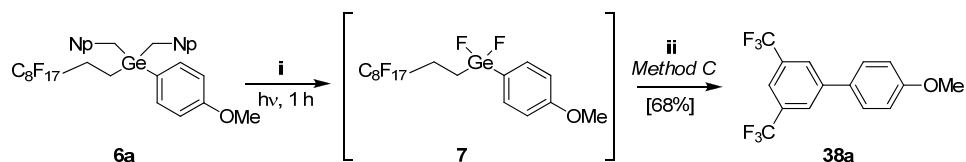


**Scheme 2.6.12.** Sequential photoactivation/cross-coupling reaction of arylgermane **6a** with 3,5-bis(trifluoromethyl)bromobenzene using Li's conditions.<sup>134</sup>

*Reagents and conditions:* i) Cu(BF<sub>4</sub>)<sub>2</sub> (4 eq.), Pyrex tube, argon purged, hv, MeOH : MeCN = 1:3, 1 h;  
ii) *Method B*: PdCl<sub>2</sub>(MeCN)<sub>2</sub> (10 mol%), P(2-Tol)<sub>3</sub> (15 mol%), 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>Br, TBAF, DMF, 120 °C, 16 h.

The addition of CuI as a co-catalyst to enhance the rate of Stille cross-coupling reactions discussed in the previous section (Scheme 2.1.11) is now generally accepted as the copper effect. This is the result of pre-transmetalation of the arylstannane component into an arylcopper intermediate which undergoes more rapid transmetalation with the ArPd<sup>II</sup>L complex than the precursor stannane itself to yield the final coupling products. It was envisaged that the germyl-Stille cross-coupling reaction could be facilitated by an analogous copper effect.

Hence, the affect of adding CuI to our germyl-Stille reaction was investigated. Difluoro arylgermane **7** was cross-coupled with 3,5-bis(trifluoromethyl)-bromobenzene using P(2-Tol)<sub>3</sub>, TBAF and PdCl<sub>2</sub>(MeCN)<sub>2</sub> in the presence of CuI as additive to give biphenyl **38a** in 68 % yield (*Method C*, Scheme 2.6.13). This yield is higher than the previous methods (*cf.* 53 % using *Method A*; 60 % using *Method B*).

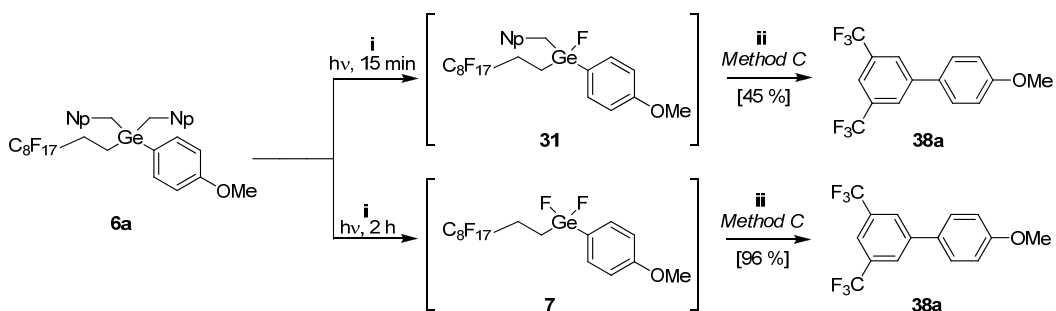


**Scheme 2.6.13.** Optimised cross-coupling of arylgermane **6a** with 3,5-bis (trifluoromethyl)bromobenzene – with CuI co-promoter.<sup>78</sup>

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$  (4 eq.), Pyrex tube, argon purged, hv, MeOH : MeCN = 1:3, 1 h; ii) *Method C*:  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%),  $\text{P}(2\text{-Tol})_3$  (15 mol%), 3,5- $(\text{CF}_3)_2\text{C}_6\text{H}_3\text{Br}$ , TBAF, CuI, DMF, 120 °C, 16 h.

Although both Gripton and Hannah (Tables 2.4.1 and 2.4.2, respectively) had concluded that two heteroatoms on the Ge centre were required for successful cross-coupling, it was considered prudent at this juncture to check that this was indeed the case for the fluorogermenes.

Consequently, mono-fluoro germane **31**, generated by short UV irradiation (~15 min) of arylgermane **6a**, was cross-coupled with 3,5-bis(trifluoromethyl)bromobenzene under *Method C* conditions to afford biphenyl **38a** in a yield of just 45 %. By contrast, cross-coupling of difluoro germane **7**, which was obtained from prolonged UV exposure until the peak corresponding to the mono-fluoro germane ( $\delta_{\text{F}}$  -203 ppm) had disappeared, under identical conditions gave the biphenyl **38a** in 96 % yield (Scheme 2.6.14).



**Scheme 2.6.14.** Reactivity of mono-fluoro and difluoro germane for cross-coupling with 3,5-bis (trifluoromethyl)bromobenzene.

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$ , Pyrex tube, argon purged, hv, MeOH : MeCN = 1:3, ii) *Method C*:  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%),  $\text{P}(2\text{-Tol})_3$  (15 mol%), 3,5- $(\text{CF}_3)_2\text{C}_6\text{H}_3\text{Br}$ , TBAF, CuI, DMF, 120 °C, 16 h.

These results demonstrated that although the mono-fluoro germane was competent for cross-coupling, its difluoro congener is a more efficient cross-coupling partner

and that provided full conversion to this reactive species is ensured by monitoring by  $^{19}\text{F}$  NMR, excellent cross-coupling yields can be attained.

The optimised photoactivation conditions were found to involve photolysis of the aryl bis(2-naphthymethyl)germanes **6** with 4 equivalents of  $\text{Cu}(\text{BF}_4)_2$  for 1 h followed by addition of another 4 equivalents of  $\text{Cu}(\text{BF}_4)_2$  and irradiation for a further 1 h (*i.e.* 2 h overall).

It is this difference in the protocol for photooxidation that accounts for the improved yield between the ‘*Method C*’ coupling in Scheme 2.6.13 and in Scheme 2.6.14 (*i.e.* 68 % vs 96 % yield).

### 2.6.2.2 Elaboration of the scope of germyl-Stille coupling reactions

Having optimised the photoactivation conditions and subsequent cross-coupling, our attention turned to delineating the scope of the germyl-Stille cross-coupling reaction. A range of *R<sub>f</sub>*-tagged arylgermanes were prepared in good yields by treating *R<sub>f</sub>*-tagged germyl bromide **40** with appropriate aryl lithium and Grignard reagents. The aryl lithium reagents were generated *in situ* by lithium-halogen exchange on aryl bromides with  $t\text{BuLi}$  (Table 2.6.2).

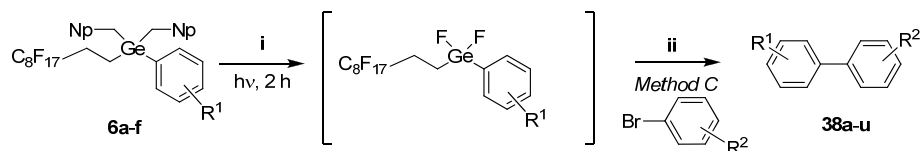
M = Li or Mg

| Entry | R <sup>1</sup>    | Product   | Yield (%)       |
|-------|-------------------|-----------|-----------------|
| 1     | 4-CH <sub>3</sub> | <b>6b</b> | 87 <sup>a</sup> |
| 2     | H                 | <b>6c</b> | 83 <sup>a</sup> |
| 3     | 4-Cl              | <b>6d</b> | 80 <sup>b</sup> |
| 4     | 2-OMe             | <b>6e</b> | 87 <sup>b</sup> |
| 5     | 4-CF <sub>3</sub> | <b>6f</b> | 84 <sup>b</sup> |

<sup>a</sup> Grignard reagent; <sup>b</sup> organolithium reagent

**Table 2.6.2.** Preparation of fluorine-tagged arylgermanes.

The optimised cross-coupling conditions (*Method C*) were then employed for the preparation various biaryls using these R<sup>f</sup>-tagged arylgermanes and various aryl bromides with electron-donating and electron-withdrawing groups (Table 2.6.3).<sup>135</sup>



| Entry | R <sup>1</sup>              | R <sup>2</sup>            | Product    | Yield (%)       |
|-------|-----------------------------|---------------------------|------------|-----------------|
| 1     | 4-OMe <b>6a</b>             | 3,5-bis(CF <sub>3</sub> ) | <b>38a</b> | 96              |
| 2     | 4-OMe <b>6a</b>             | 4-Cl                      | <b>38b</b> | 85              |
| 3     | 4-OMe <b>6a</b>             | 4-benzoxy                 | <b>38c</b> | 65              |
| 4     | 4-OMe <b>6a</b>             | 1-naphthylene             | <b>38d</b> | 74              |
| 5     | 4-CH <sub>3</sub> <b>6b</b> | 3,5-bis(CF <sub>3</sub> ) | <b>38e</b> | 84              |
| 6     | 4-CH <sub>3</sub> <b>6b</b> | 4-Cl                      | <b>38f</b> | 69              |
| 7     | 4-CH <sub>3</sub> <b>6b</b> | 4-benzoxy                 | <b>38g</b> | 48              |
| 8     | 4-CH <sub>3</sub> <b>6b</b> | 1-naphthylene             | <b>38h</b> | 71              |
| 9     | H <b>6c</b>                 | 3,5-bis(CF <sub>3</sub> ) | <b>38i</b> | 74              |
| 10    | H <b>6c</b>                 | 4-Cl                      | <b>38j</b> | 63              |
| 11    | H <b>6c</b>                 | 4-benzoxy                 | <b>38k</b> | 40              |
| 12    | H <b>6c</b>                 | 1-naphthylene             | <b>38l</b> | 60              |
| 13    | 4-Cl <b>6d</b>              | 3,5-bis(CF <sub>3</sub> ) | <b>38m</b> | 71              |
| 14    | 4-Cl <b>6d</b>              | 4-benzoxy                 | <b>38n</b> | 42              |
| 15    | 4-Cl <b>6d</b>              | 1-naphthylene             | <b>38o</b> | 75              |
| 16    | 2-OMe <b>6e</b>             | 3,5-bis(CF <sub>3</sub> ) | <b>38p</b> | 65              |
| 17    | 2-OMe <b>6e</b>             | 4-Cl                      | <b>38q</b> | 57              |
| 18    | 2-OMe <b>6e</b>             | 4-benzoxy                 | <b>38r</b> | 11 <sup>*</sup> |
| 19    | 2-OMe <b>6e</b>             | 1-naphthylene             | <b>38s</b> | 27              |
| 20    | 4-CF <sub>3</sub> <b>6f</b> | 3,5-bis(CF <sub>3</sub> ) | <b>38t</b> | 26 <sup>*</sup> |
| 21    | 4-CF <sub>3</sub> <b>6f</b> | 4-Cl                      | <b>38u</b> | 11 <sup>*</sup> |

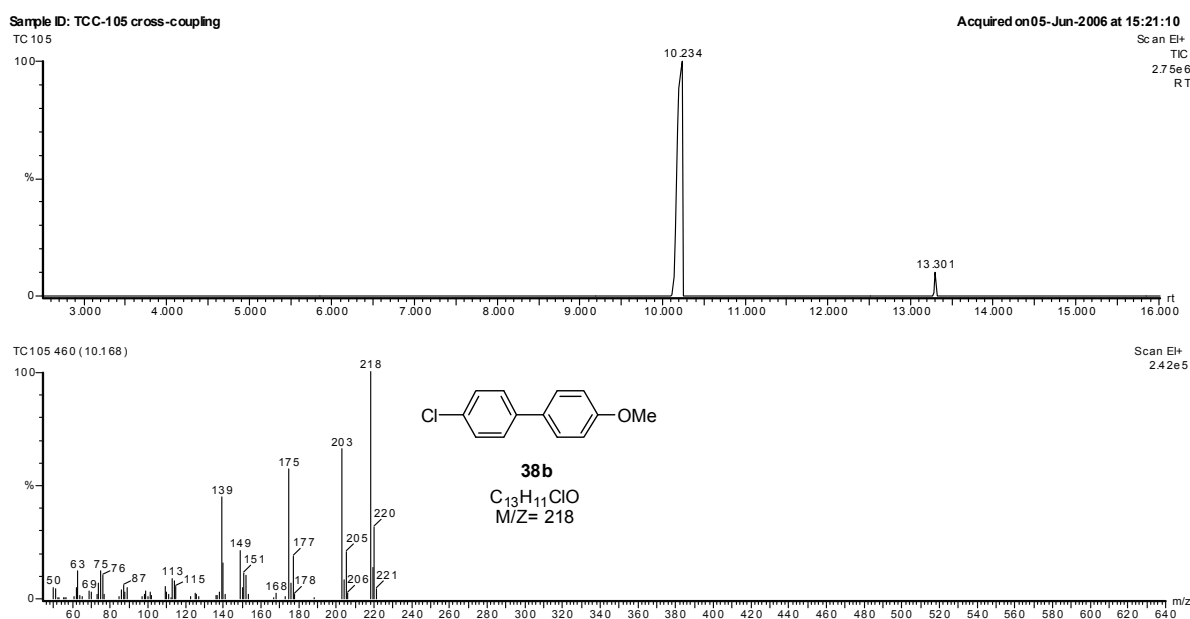
\* GC-MS yield

**Table 2.6.3.** Scope of germyl-Stille type photoactivation/cross-coupling reactions with various R<sup>f</sup>-tagged arylgermane and aryl bromides.<sup>135</sup>

*Reagents and conditions:* i) Cu(BF<sub>4</sub>)<sub>2</sub> (4+4 eq.), Pyrex tube, argon purged, hν, MeOH : MeCN = 1:3, 2 h; ii) *Method C:* PdCl<sub>2</sub>(MeCN)<sub>2</sub> (10 mol%), P(2-Tol)<sub>3</sub> (15 mol%), TBAF, CuI, DMF, 120 °C, 16 h.

By employing these optimised cross-coupling conditions with efficient photoactivation much better results were achieved than previously. For example, the yield of biphenyl **38a** was 96 % over two steps (entry 1) and the yield of biphenyl **38d** was raised to 74 % (*cf.* 15 % by Hannah;<sup>121</sup> entry 4). Importantly, it emerged from this work that the photoactivation process displayed no significant time-dependence as a function of the electronic nature of the arylgermane substrates. This obviates the need to optimise the photolysis period for each substrate; the 2 h protocol is generally suitable.

The selectivity of this reaction for cross-coupling of aryl bromides over aryl chlorides is revealed by examination of the case of 1-bromo-4-chlorobenzene (entry 2) which gave 4-chloro-4'-methoxy-1,1'-biphenyl **38b** exclusively; no 4-bromo-4'-methoxy-1,1'-biphenyl could be detected by GC-MS (Figure 2.6.5).



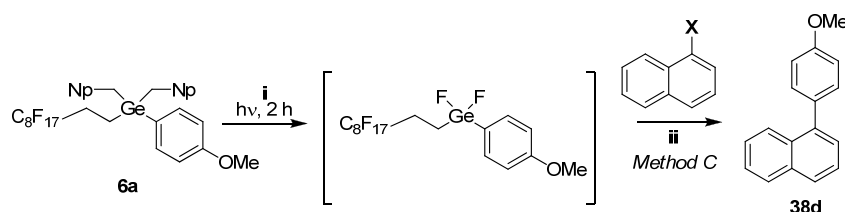
*NB:* the peak with retention time 13.301 min is the phosphine ligand.

**Figure 2.6.5.** GC-MS chromatogram and mass spectrum of 4-chloro-4'-methoxy-1,1'-biaryl **38b**.

The MS parent peaks (M<sup>+</sup>) for the 4-chloro-4'-methoxy-1,1'-biaryl **38b** is at *m/z* 218/220 with an unambiguous 3 to 1 peak ratio due to the isotope pattern of chlorine (<sup>35</sup>Cl : <sup>37</sup>Cl).

The overall trend relating the electronic nature of the reaction partners for germyl-Stille coupling revealed by Table 2.6.3 is congruous with the general situation found in Stille and Hiyama cross-coupling reactions: (a) electron-withdrawing groups on the aryl bromide result in higher yields of biphenyls (*cf.* entries 1-3 and 5-7); (b) electron-donating groups on the fluorous-tagged arylgermane result in higher yields of biphenyls (*cf.* entries 1-3 and 9-11) with the exception of the 2-OMe substituent for which steric hindrance interferes (*cf.* entries 1-4 and 16-19). With strong electron-withdrawing groups on the arylgermane, inferior yields of biphenyls are obtained (*e.g.* entries 20 and 21).

To explore the compatibility of germyl-Stille cross-coupling with alternative aryl (pseudo)halide electrophiles, R<sub>f</sub>-tagged arylgermane **6a** was employed as a substrate for photoactivation/cross-coupling with 1-naphthyl chloride, -iodide and -triflate under *Method C* conditions using LiCl as an additive. The resulting biaryl **38d** was quantified by GC/MS using the common by-product, 2-(methoxymethyl)naphthalene **38d** from the photolysis as an internal standard (Table 2.6.4).



| Entry | X   | Yield (%) <sup>a</sup> |
|-------|-----|------------------------|
| 1     | Cl  | < 1 <sup>a</sup>       |
| 2     | Br  | 74 <sup>b</sup>        |
| 3     | I   | 12 <sup>a</sup>        |
| 4     | OTf | -                      |

<sup>a</sup> GC yield; <sup>b</sup> isolated yield; used for calibration the GC/MS outcomes

**Table 2.6.4.** Screening for compatibility of the germyl-Stille cross-coupling with various aryl (pseudo)halides.

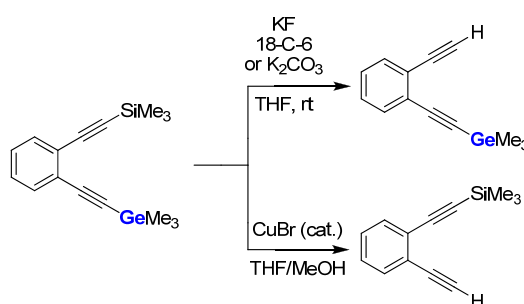
*Reagents and conditions:* i) Cu(BF<sub>4</sub>)<sub>2</sub> (4+4 eq.), Pyrex tube, argon purged, hv, MeOH : MeCN = 1:3, 2 h; ii) *Method C*: PdCl<sub>2</sub>(MeCN)<sub>2</sub>, P(2-Tol)<sub>3</sub>, TBAF, CuI, LiCl, DMF, 120 °C, 16 h.

In the light of the aforementioned chemoselective coupling of 1-bromo-4-chlorobenzene substrate (*cf.* Figure 2.6.5), it was not surprising to find that no significant amount of biaryl **38d** was detected when the aryl chloride was employed

as a coupling partner (entry 1). Cross-coupling with the aryl iodide gave a surprisingly poor yield of 12 % (entry 3 *cf.* 74% for the bromide). In addition, the aryl triflate was found to be unreactive towards this cross-coupling protocol (entry 4).

### 2.6.2.3 Exploration of the stability profiles of R<sup>f</sup>-tagged arylgermanes

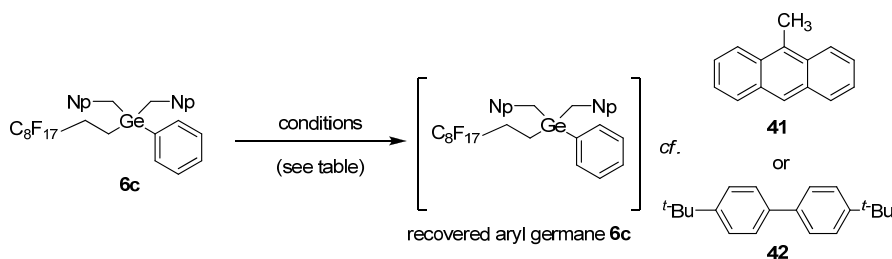
As discussed above, better chemical tolerance of the C-Ge bond in comparison with C-Si and C-Sn bonds is expected due to the lesser polarity across C-Ge bonds as compared to the other two bonds. Vasella exploited these differences to demonstrate the orthogonal deprotection of trimethylsilyl (TMS) and trimethylgermyl (TMG) protected diynes. The TMS group was removed under fluoridolytic and basic conditions whereas the TMG group was removed upon treatment with CuBr in THF/MeOH (Scheme 2.6.15).<sup>136</sup>



**Scheme 2.6.15.** Vasella's demonstration of selective removal of TMG and TMS-protected alkynes.<sup>136</sup>

Turner (Spivey group, 2000-2003)<sup>137</sup> also showed that  $\alpha$ -silyl and  $\alpha$ -germyl thiophenes could be orthogonally deprotected using fluoride and acid respectively.<sup>138</sup>

A systematic study of the stability of our R<sup>f</sup>-tagged arylgermanes was carried out using common reaction conditions, encountered during synthesis. 9-Methylantracene **41** and 4,4'-di-*tert*-butyl-1,1'-biphenyl **42** were used as internal standards.<sup>139,140</sup> All reactions employed 5 equivalents of reagents at RT for 3 h and were analysed by HPLC. The ratio of the peak areas was quantified between arylgermane **6c** and internal standards **41** or **42**. The percentage recovery of germane **6c** was compared to blank controls in the appropriate solvent (Table 2.6.5).



| Entry | Conditions                                | Internal Standard | Average recovery of <b>6c</b> (%) |
|-------|-------------------------------------------|-------------------|-----------------------------------|
| 1     | Mercaptoethanol<br>DBU, DMF               | <b>41</b>         | 102                               |
| 2     | 20 % Piperidine, DMF                      | <b>41</b>         | 101                               |
| 3     | 2 % Hydrazine, DMF                        | <b>41</b>         | 104                               |
| 4     | NaBH <sub>4</sub> , THF                   | <b>41</b>         | 107                               |
| 5     | LiAlH <sub>4</sub> , THF                  | <b>41</b>         | 104                               |
| 6     | TBAF, THF                                 | <b>41</b>         | 102                               |
| 7     | 50 % TFA, CH <sub>2</sub> Cl <sub>2</sub> | <b>41</b>         | 20                                |
| 8     | 3-CPBA, CH <sub>2</sub> Cl <sub>2</sub>   | <b>42</b>         | 76                                |

*N.B.* The recovery was averaged for two runs.; Deviation is set at  $\pm 15$  % (see experimental section)

*HPLC conditions:* Column: XTerra RP-8, 4.6 mm  $\times$  150mm, 5 $\mu$ ; mobile phase: MeCN/H<sub>2</sub>O = 80:20; flow rate = 1ml/min; Detection at 245 nm; injection volume: 2 $\mu$ L.

**Table 2.6.5.** Stability tests on arylgermane **6c**.

Inspection of Table 2.6.5 reveals that arylgermane **6c** can tolerate basic, reductive and several common deprotection conditions (entries 1-5). The inertness of the arylgermane linkage to these conditions is notable and contrasts with the poor stability of arylstannanes and arylsilanes. Most importantly, the arylgermane is chemically inert towards exposure to fluoride ions (entry 6). This profile provides compatibility with fluoridolytic conditions for deprotection of silyl ethers. It is expected that this will allow these derivatives to be used for the synthesis of complex target molecules. However, the compound was partially degraded by strong acid (50% trifluoroacetic acid/CH<sub>2</sub>Cl<sub>2</sub>, entry 7) and oxidative conditions (3-CPBA/CH<sub>2</sub>Cl<sub>2</sub>, entry 8). Nevertheless, *Rf*-tagged arylgermanes are envisaged to be stable towards exposure to just 1 equivalent of 3-CPBA or other oxidants at low temperature.

#### 2.6.2.4 Conclusions

New conditions for germyl-Stille cross-coupling reactions have been developed and have been found to give better results than previously. Optimised photoactivation conditions were found which were appropriate for all substrates tested.

A survey of the electronic and steric requirements for cross-coupling shows that the best coupling partners are electron-rich arylgermanes and electron-poor aryl bromides. However, almost all combinations will couple in reasonable yields. Furthermore, the stability of arylgermanes towards nucleophilic, basic and reductive conditions (but not acidic and oxidative conditions) should make these derivatives of significant utility in synthesis.

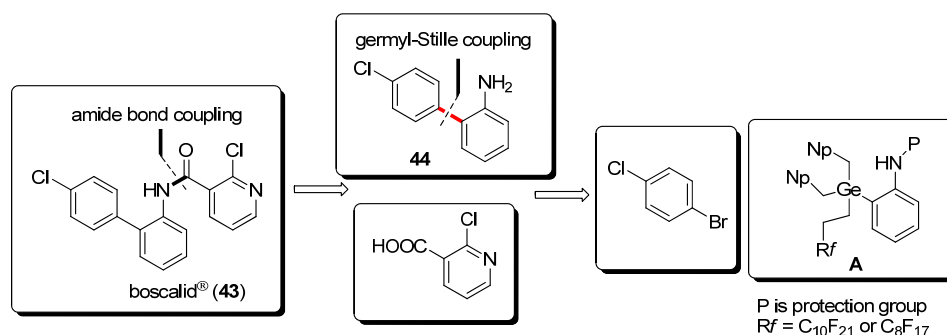
In the next section, our endeavours to demonstrate the utility of this new method for the synthesis of some agrochemical fungicides are described.

#### 2.6.3 Towards the synthesis of boscalid by germyl-Stille cross-coupling

Boscalid (**43**) is a versatile fungicide designed and commercialised by BASF.<sup>141</sup> It is widely used on food crops such as lettuce, beans, berries, bulb vegetables, carrots and fruiting vegetables primarily as protection against *Sclerotinia* drop disease.<sup>142</sup> Boscalid targets an enzyme in fungi's mitochondria named succinate ubiquinone reductase, which is part of the electron transport complex II. As part of the oxidative phosphorylation pathway, complex II effects dehydrogenation of succinate with concomitant formation of ubiquinol (UQH<sub>2</sub>) from ubiquinone (UQ).<sup>143</sup> Boscalid inhibits this electron transfer pathway and consequently the energy respiration cycle resulting in cell death. In addition, complex II also participates in the citric acid cycle, which supplies precursors for amino acid synthesis and other building blocks. Therefore, boscalid acts a dual-functional fungicide significantly reducing the risk of cross-resistance.

Boscalid and its analogues were considered interesting target molecules to underscore the robustness of arylgermane derivatives and demonstrate the concept of iterative chemical synthesis using phase-tagged substrates. Analysis of the skeleton of boscalid reveals a biaryl aniline subunit which forms an amide bond with a 2-chloronicotinic acid unit. It was proposed to construct the biaryl aniline subunit by

employing a germyl Stille cross-coupling (Scheme 2.6.16).



**Scheme 2.6.16.** Proposed disconnection for boscalid (43).

At the outset, it was planned to prepare an *N*-protected *ortho*-aniline containing arylgermane, to cross-couple this compound with 1-bromo-4-chlorobenzene, to deprotect the aniline nitrogen to give 2-amino-4'-chlorobiphenyl **44** and then to complete the synthesis by amide coupling with 2-chloronicotinic acid.

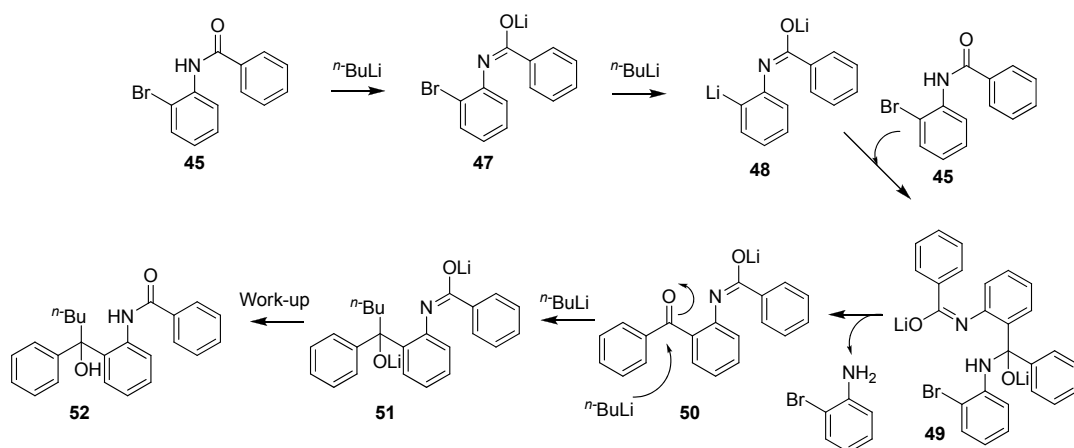
Before attempting this synthesis, it was decided to prepare an authentic sample of 2-amino-4'-chlorobiphenyl **44** by coupling *N*-benzoyl-2-trimethylstannyl aniline **46** with 1-bromo-4-chlorobenzene using a Stille coupling process. To this end, *N*-benzoyl-2-bromoaniline **45** was treated with *n*-butyllithium in THF at -100 °C and then trimethylstannyl chloride was added to quench the resulting aryllithium species (Scheme 2.6.17).<sup>144</sup>



**Scheme 2.6.17.** Attempted synthesis of *N*-benzoyl-2-trimethylstannyl aniline **46**.

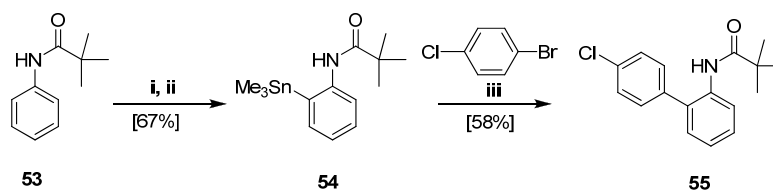
*Reagents and conditions:* i) *n*BuLi (2.5 eq.), THF, -100 °C, 30 min; ii) Me<sub>3</sub>SnCl, -100 °C to RT, 2 h.

However, analysis of the MS fragmentation pattern and the <sup>1</sup>H and <sup>13</sup>C NMR spectra of the resulting reaction mixture revealed that the product was in fact *N*-(2-(1-hydroxy-1-phenylpentyl)phenyl)benzamide **52**. A possible mechanism for its formation is shown below (Scheme 2.6.18).



**Scheme 2.6.18.** Proposed mechanism of formation of *N*-(2-(1-hydroxy-1-phenylpentyl)-phenyl)benzamide **52**.

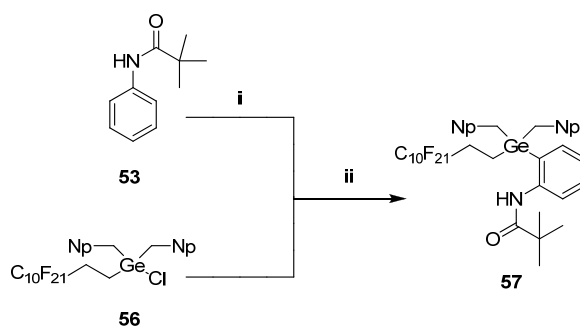
This reaction pathway could not be prevented by the use of Barbier conditions (in which the  $\text{Me}_3\text{SnCl}$  was present prior to addition of the  $n\text{-BuLi}$ ) so we explored direct *ortho*-lithiation of *N*-pivaloylanilide.<sup>145</sup> Thus, 2-trimethylstannyl-*N*-pivaloylanilide **54** was produced in 67 % yield by treatment of *N*-pivaloylanilide **53** with *n*-butyllithium followed by quenching with trimethylstannyl chloride.<sup>146,147</sup> To obtain the authentic biphenyl **55**, and also to compare the relative reactivity towards cross-coupling of organostannes and organogermanes, 2-trimethylstannyl pivalanilide **54** was cross-coupled with 4-chloro-bromobenzene using the conditions of Baldwin to give biphenyl **55** in 58 % yield (Scheme 2.6.19).<sup>148</sup>



**Scheme 2.6.19.** Synthesis of the authentic biphenyl **55** by direct lithiation followed by Stille cross-coupling

*Reagents and conditions:* i)  $n\text{-BuLi}$  (2.5 eq.), TMEDA, THF, 0 °C, 2.5 h; ii)  $\text{Me}_3\text{SnCl}$  (2 eq.), 0 °C to RT, 16 h; iii) i)  $\text{Pd}(\text{PPh}_3)_4$ , CsF, CuI, DMF, 40 °C, 16 h.

Following this successful preparation of the trimethylstannyl pivalanilide **54**, the same approach was explored for synthesis of the corresponding arylgermane **57** (Scheme 2.6.20).<sup>145</sup>

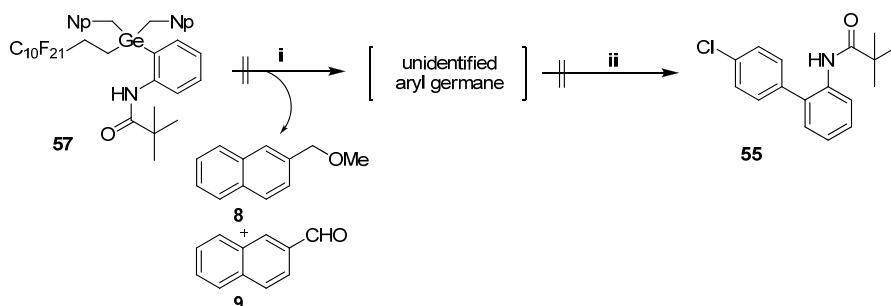


**Scheme 2.6.20.** Preparation of 2-pivalanilidyl fluororous-tagged arylgermane **57**.

*Reagents and conditions:* i)  $n\text{BuLi}$  (2.5 eq.), TMEDA, THF, 0 °C, 2.5 h; ii) 0 °C to RT, 16 h

The reaction was successful but a by-product containing an *n*-butyl group contaminated the desired 2-pivalanilidyl fluororous-tagged arylgermane **57** as evidenced by many aliphatic signals in the region between  $\delta$  1.0 and 1.5 ppm in the  $^1\text{H}$  NMR spectrum.

Although contaminated with this unidentified by-product, germane **57** was subjected to photolysis under the usual conditions. However, neither of the two key by-products, 2-(methoxymethyl)naphthalene **8** and 2-naphthaldehyde **9**, could be detected by TLC or GC-MS. Instead, the photolysis reaction gave an unknown product with high polarity rather than activated difluoro germane. Nevertheless, the mixture of products was subjected to cross coupling with 4-chlorobromobenzene using the standard coupling conditions. By comparing the  $^1\text{H}$  NMR spectrum of the reaction mixture with that of the authentic product biphenyl **55**, it was clear that no cross-coupling had occurred (Scheme 2.6.21).

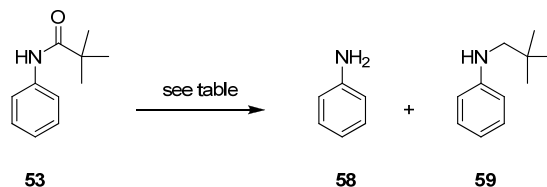


**Scheme 2.6.21.** Attempted synthesis of biphenyl **55** via germynl-Stille cross-coupling.

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$  (4 eq.), Pyrex tube, Argon purged,  $h\nu$ , MeOH : MeCN = 1:3, 1 h; ii) *Method A*:  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%), dppp (15 mol%), 4- $\text{ClC}_6\text{H}_4\text{Br}$ , KF, DMF, 120 °C, 16 h.

The most likely cause of this failure of the photolysis reaction was considered to be the presence of the amide function and so it was decided to remove the *N*-pivaloyl

group to allow cross-coupling of the unprotected aniline derivative. Consequently, we next explored conditions for removal of the *N*-pivaloyl group using *N*-pivaloylanilide **53** as a model substrate (Table 2.6.6)

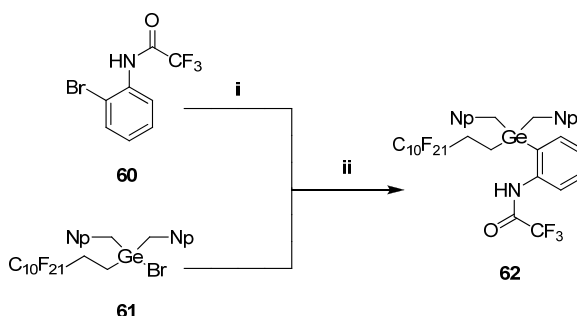


| Entry | Conditions                                                                          | Outcome                                                                                     |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| 1     | 3N HCl <sub>(aq)</sub> / dioxane<br>100 °C, 16 h <sup>149</sup>                     | ~ 50% conversion;<br>aniline <b>58</b> , no amine <b>59</b>                                 |
| 2     | 10 M HCl / EtOH<br>80 °C, 16 h <sup>150</sup>                                       | ~ 50% conversion;<br>aniline <b>58</b> , no amine <b>59</b>                                 |
| 3     | 48 % HBr <sub>(aq)</sub> / EtOH<br>80 °C, 16 h <sup>151</sup>                       | ~ 50% conversion;<br>aniline <b>58</b> , no amine <b>59</b>                                 |
| 4     | 35 % H <sub>2</sub> SO <sub>4</sub><br>EtOH, 80 °C, 16 h <sup>152</sup>             | > 50% conversion;<br>aniline <b>58</b> , no amine <b>59</b>                                 |
| 5     | LiAlH <sub>4</sub><br>THF, 0 °C ~ reflux, 3 h <sup>153</sup>                        | 100 % conversion,<br>trace of aniline <b>58</b> , amine <b>59</b><br>was the major product. |
| 6     | LiAlH <sub>4</sub><br>THF, 0 °C ~ RT, 16 h <sup>153</sup>                           | 100 % conversion,<br>trace of aniline <b>58</b> , amine <b>59</b><br>was the major product. |
| 7     | H <sub>2</sub> NNH <sub>2</sub><br>EtOH, 120 °C, sealed tube<br>16 h <sup>154</sup> | < 20% conversion;<br>No aniline <b>58</b> ,<br>trace of amine <b>59</b>                     |

**Table 2.6.6.** Attempted deprotection of pivalanilide **53**.

*N*-Pivaloylanilide **53** was treated with 3N HCl in dioxane, 10M HCl in EtOH, 48% HBr<sub>(aq)</sub> in EtOH and 35% H<sub>2</sub>SO<sub>4</sub> in EtOH at reflux (entries 1-4).<sup>153</sup> However, in all cases only ~ 50 % of the *N*-pivaloylanilide **53** was deprotected to give aniline **58** after 16 h. By contrast, *N*-pivaloylanilide **53** was reduced with LiAlH<sub>4</sub> to afford amine **59** in high yield (entries 5 and 6).<sup>153</sup> In addition, attempted deprotection using hydrazine, resulted in less than 20 % of *N*-pivaloylanilide **53** being converted to give traces of amine **59** but no aniline **58** (entry 7).<sup>154</sup> Since none of these deprotection conditions were efficient we decided to employ an alternative *ortho*-directing aniline derivative.

The trifluoroacetyl amide of aniline was envisioned to be deprotected more readily than its pivaloyl analogue. Thus, 2-bromotrifluoroacetanilide **60** was prepared by treatment of 2-bromoaniline with trifluoroacetic anhydride in 95 % yield. 2-Bromo-trifluoroacetanilide **60** was then deprotonated with MeLi (1 eq.) at -78 °C, treated with <sup>t</sup>BuLi (2.2 eq) to effect bromine-lithium exchange, and then reacted with fluorine-tagged germyl bromide **61** to afford 2-trifluoroacetanilidyl fluorine-tagged arylgermane **62** (Scheme 2.6.22).<sup>155</sup>

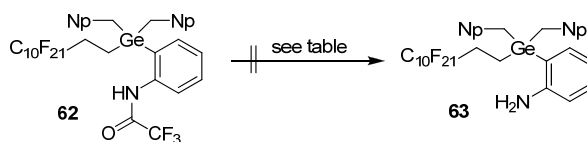


**Scheme 2.6.22.** The preparation of 2-trifluoroacetanilidyl fluorine-tagged arylgermane **62**.

*Reagents and conditions:* i) MeLi (1 eq.), <sup>t</sup>BuLi (2.2 eq.), -78 °C, 30 min ; ii) -78 °C to RT, 16 h.

The germyl bromide **61** was used in this reaction because Catherine Noban (Spivey group 2001-2005)<sup>156</sup> had found that germyl bromides often give better results than germyl chlorides as electrophiles with organolithium reagents. Again, the product was contaminated with an unidentified aliphatic containing by-product. Nevertheless, the MS spectrum showed a strong peak at *m/z* 950 (M-141) corresponding to the expected mass ion of the product following loss of a naphthylmethyl group.

It was hoped that the unknown by-product might be separable after removal of the trifluoroacetyl group. Consequently, 2-trifluoroacetanilidyl fluorine-tagged arylgermane **62** was subjected to several deprotecting conditions to achieve hydrolysis of the trifluoroacetyl group (Table 2.6.7).

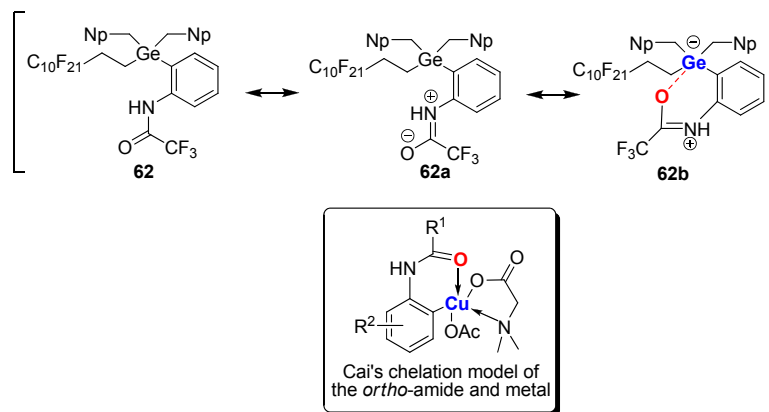


| Entry | Conditions                                            | Time   | Outcome     |
|-------|-------------------------------------------------------|--------|-------------|
| 1     | K <sub>2</sub> CO <sub>3(s)</sub><br>MeOH, rt         | 2 days | No reaction |
| 2     | Sat. K <sub>2</sub> CO <sub>3(aq)</sub><br>THF, 40 °C | 16 h   | No reaction |
| 3     | 40 % NaOH <sub>(aq)</sub><br>TBAI, THF, 60 °C         | 2 days | No reaction |

**Table 2.6.7.** Attempted deprotection of 2-trifluoroacetanilidyl fluororous-tagged arylgermane **62**.

None of these conditions effected to hydrolysis of the 2-trifluoroacetanilidyl R<sub>f</sub>-tagged arylgermane **62**, whereas an individual qualitative study of deprotection of 2-bromotrifluoroacetanilide **60** proceeded smoothly under the conditions described in entry 2.

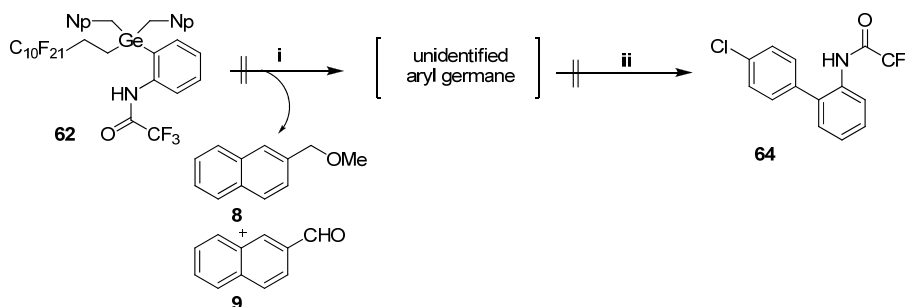
In 2006, Cai proposed that strong chelation between an *ortho*-amide and a main group metal could strongly impede hydrolysis.<sup>157</sup> It is possible that the trifluoroacetyl group in arylgermane **62**, being *ortho* to the germanium centre, is particularly resistant to hydrolysis due to this effect (Scheme 2.6.23).<sup>157</sup>



**Scheme 2.6.23.** Proposed association between the trifluoroacetamide carbonyl and the trialkylgermanium centre in arylgermane **62** and Cai's chelation model.<sup>157</sup>

The 2-trifluoroacetanilidyl fluororous-tagged arylgermane **62** itself was subjected to photolysis in the presence of Cu(BF<sub>4</sub>)<sub>2</sub> under the usual conditions. As for the corresponding 2-pivalanilidyl fluororous-tagged arylgermane **57**, the key side-products 2-(methoxymethyl)naphthalene **8** and 2-naphthaldehyde **9** could not be detected by

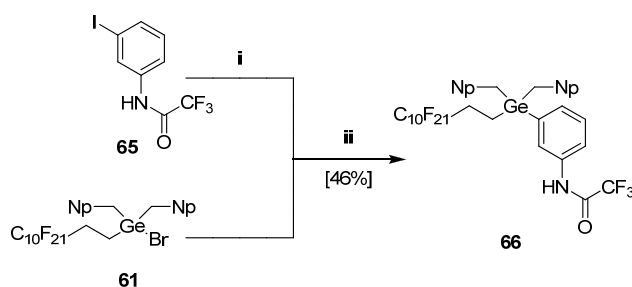
TLC or GC-MS and a high polarity product was found. The unknown compound was subsequently employed crude for cross coupling with 1-bromo-4-chlorobenzene under standard conditions. However, no biphenyl **64** could be found after purification by column chromatography (Scheme 2.6.24).



**Scheme 2.6.24.** Attempted synthesis of biphenyl **64** via germyl-Stille cross-coupling.

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$  (4 eq.), Pyrex tube, argon purged, hv, MeOH : MeCN = 1:3, 1 h;  
ii) *Method A:*  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%), dppp (15 mol%), 4- $\text{ClC}_6\text{H}_4\text{Br}$ , KF, DMF, 120 °C, 16 h.

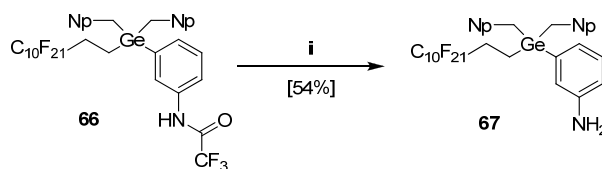
To circumvent the difficult hydrolysis of the *ortho*-trifluoroacetyl group in 2-trifluoroacetanilidyl fluororous-tagged arylgermane **62** and to substantiate the proposed chelation as being the reason for its resistance to photolysis, the 3-trifluoroacetanilidyl fluororous-tagged arylgermane **66** was prepared by deprotonation of 3-iodo-trifluoroacetanilide **65** with NaH at RT, treatment with  $t\text{BuLi}$  at -100 °C to effect iodine-lithium exchange, and then reaction with germyl bromide **61** in THF. The mixture was left for 16 h at RT to give 3-trifluoroacetanilidyl fluororous-tagged arylgermane **66** in 46 % yield (Scheme 2.6.25).



**Scheme 2.6.25.** The preparation of 3-trifluoroacetanilidyl fluororous-tagged arylgermane **66**.

*Reagents and conditions:* i) NaH 60 % in mineral oil (1 eq.), RT, 1 h,  $t\text{BuLi}$  (2.2 eq.), -100 °C, 30 min ;  
ii) -78 °C to RT, 16 h.

The 3-trifluoroacetanilidyl fluororous-tagged arylgermane **66** was successfully hydrolysed under basic conditions using TBAI as phase-transfer catalyst at 60 °C for 2 days forming 3-amino fluororous-tagged arylgermane **67** in 54 % yield (Scheme 2.6.26).



**Scheme 2.6.26.** The hydrolysis of 3-trifluoroacetanilidyl fluororous-tagged arylgermane **66**.

*Reagents and conditions:* i) 40 % NaOH<sub>(aq)</sub>, TBAI, THF, 60 °C, 48 h.

This deprotection of the *N*-trifluoroacetyl group emphasises the stability of arylgermanes under strongly basic conditions for prolonged periods of time which is in contrast to organosilane and organostannane congeners which would not be compatible with these conditions. Moreover, the success of this deprotection, and not the previous one, lends credence to the notion that there is a stabilising interaction between the Ge centre and the amide when these are situated *ortho* to each other (although this could conceivably also be a steric effect).

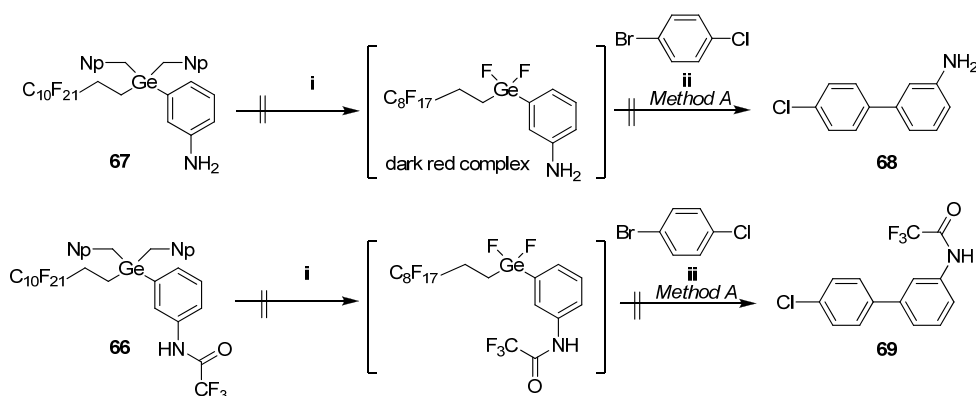
Unfortunately, 3-amino fluororous-tagged arylgermane **67** reacted with Cu(BF<sub>4</sub>)<sub>2</sub> in the photolysis reaction resulting in the solution turning dark red. This is probably due to the free amine coordinating tightly to the Cu(II). To verify this hypothesis some control reactions were performed with 3-iodo-trifluoroacetanilide, trifluoroacetanilide and aniline itself (Table 2.6.8).

| Entry | Substrate                   | Reagent                           | Outcome                                  |
|-------|-----------------------------|-----------------------------------|------------------------------------------|
| 1     | 3-Iodo-trifluoroacetanilide | Cu(BF <sub>4</sub> ) <sub>2</sub> | No colour change<br>(pale blue solution) |
| 2     | Trifluoroacetanilide        | Cu(BF <sub>4</sub> ) <sub>2</sub> | No colour change<br>(pale blue solution) |
| 3     | Aniline                     | Cu(BF <sub>4</sub> ) <sub>2</sub> | solution turns dark red                  |

**Table 2.6.8.** Treatment of various anilines with Cu(BF<sub>4</sub>)<sub>2</sub> in MeCN.

Only the unprotected aniline interacted with Cu(II) to afford a red solution (entry 3). The protected amines were inert (entries 1 and 2).

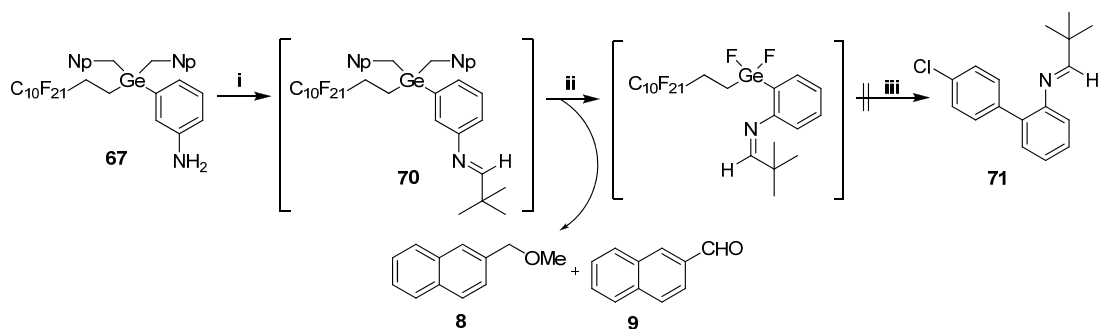
Despite the formation of the dark red coloured Cu(II)-3-amino fluororous-tagged arylgermane complex, the photolysis reaction was carried out as usual followed by attempted cross-coupling with 1-bromo-4-chlorobenzene. No desired biphenyl product could be detected by GC-MS. The same outcome was obtained using the 3-trifluoroacetanilidyl fluororous-tagged arylgermane **66** as a substrate for the same sequential photoactivation/cross-coupling protocol (Scheme 2.6.27).



**Scheme 2.6.27.** Attempted synthesis of biphenyls **68** and **69** via germyl-Stille cross-coupling.

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$  (4 eq.), Pyrex tube, argon purged,  $h\nu$ ,  $\text{MeOH} : \text{MeCN} = 1:3$ , 1 h;  
 ii) *Method A*: 1-bromo-4-chlorobenzene,  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%), dppp (15 mol%), KF, DMF, 120 °C, 16 h

To avoid the complex formation between Cu(II) and the 3-amino fluororous-tagged arylgermane **67**, the free amine group was protected with pivalaldehyde catalyzed by 4-TsOH and molecular sieves (3 Å) to give imine protected fluororous-tagged arylgermane **70**.<sup>158</sup> Imine protected fluororous-tagged arylgermane **70** was then subjected to photolysis without further purification; there was no colour change. The residue was injected into the GC-MS to confirm that the key by-products, 2-(methoxymethyl)naphthalene **8** and 2-naphthaldehyde **9** had been formed. There were traces of these compounds present so the product mixture was subjected to cross-coupling in the usual manner. However, no desired biphenyl **71** could be detected by GC-MS after purification by column chromatography (Scheme 2.6.28).

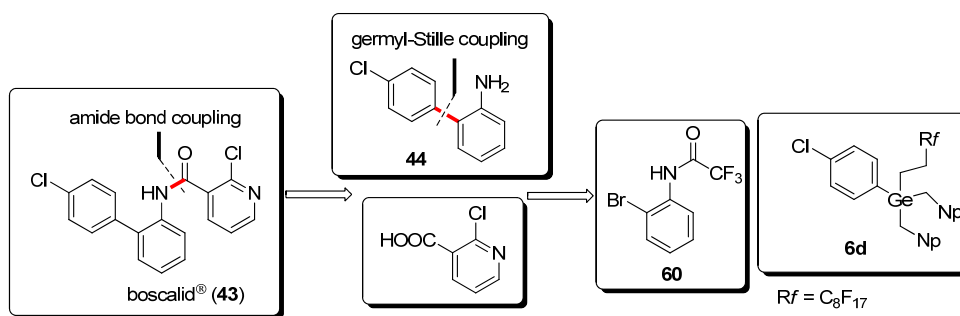


**Scheme 2.6.28.** *In situ* protection/activation/attempted cross-coupling of 3-pivalylimineyl fluororous-tagged arylgermane **70**.

*Reagents and conditions:* i) pivalaldehyde, 4-TsOH, 3 Å M.S, CH<sub>2</sub>Cl<sub>2</sub>, RT, 48 h; ii) Cu(BF<sub>4</sub>)<sub>2</sub> (4 eq.), Pyrex tube, Argon purged, hν, MeOH : MeCN = 1:3, 1 h; iii) *Method A*: PdCl<sub>2</sub>(MeCN)<sub>2</sub> (10 mol%), dppp (15 mol%), 4-ClC<sub>6</sub>H<sub>4</sub>Br, KF, DMF, 120 °C, 16 h.

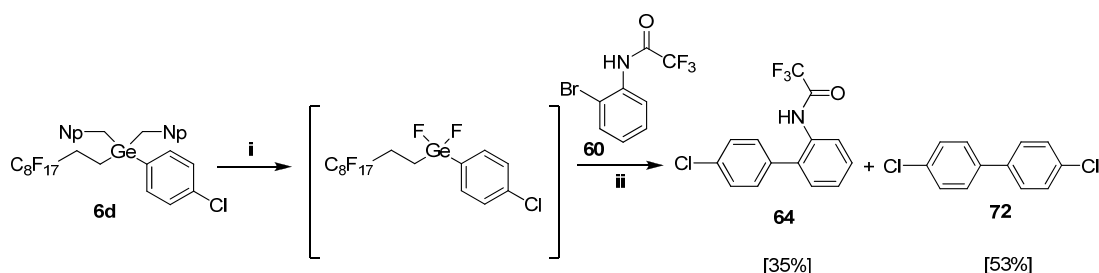
It was disappointing that none of the aniline derivatives would undergo photolysis/cross-coupling. The reason is probably because of inhibition of the photoactivated electron-transfer by the amine or acetamide group on the fluororous-tagged arylgermane.

A new approach was clearly required and so the following revised strategy for the synthesis of boscalid (**43**) was proposed. In this approach, it was planned to employ *R<sub>f</sub>*-tagged 4-chloro-arylgermane **6d** as a substrate for coupling with 2-bromo-*N*-trifluoroacetamide **60** to form biphenyl **44** (Scheme 2.6.29).



**Scheme 2.6.29.** Revised disconnection for boscalid (**43**).

The photolysis/cross-coupling of 4-chloro fluororous-tagged arylgermane **6d** under the usual conditions gave the desired biphenyl **64** in 35 % yield along with homo-coupling product, 4,4'-dichlorobiphenyl **72** as the major product (53 % yield, Scheme 2.6.30).

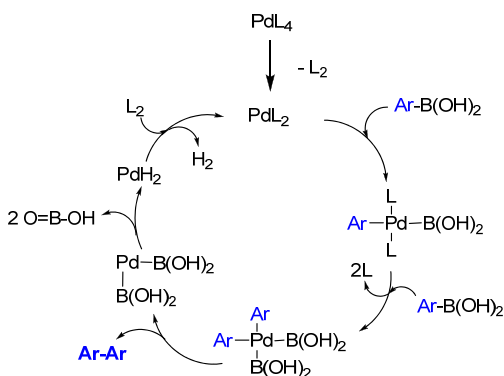


**Scheme 2.6.30.** Synthesis of the biphenyl **64**.

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$  (4 eq.), Pyrex tube, argon purged, hv, MeOH : MeCN = 1:3, 1 h;  
 ii) *Method C*:  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%),  $\text{P}(2\text{-Tol})_3$  (15 mol%), CuI, TBAF, DMF, 120 °C, 16 h.

4,4'-Dichlorobiphenyl **72** was the first homo-coupling product that we had identified from self-coupling of a fluorous-tagged arylgermane. In the literature, Suzuki homo-coupling reactions have been studied by Wong<sup>159</sup> and by Marcial;<sup>160</sup> and Stille self-coupling reactions have been investigated by Farina.<sup>66</sup>

A catalytic cycle for the arylboronic acid-based homo-coupling reaction was proposed by Marcial (Scheme 2.6.31).<sup>160</sup>

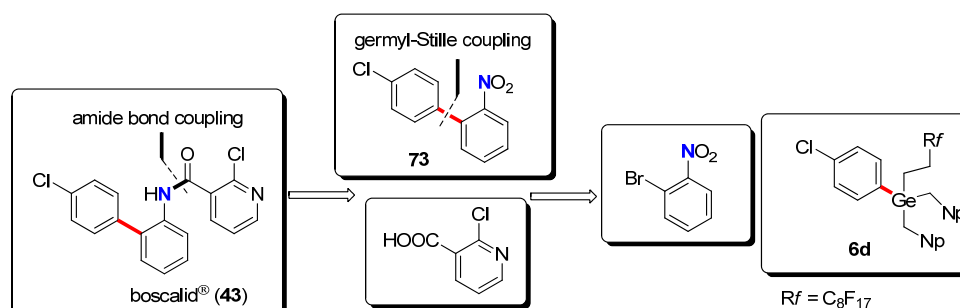


**Scheme 2.6.31.** Marcial's mechanism for Suzuki homo-coupling.<sup>160</sup>

The homo-coupling pathway is considered to be oxidative coupling and takes place when the rate of cross-coupling is relatively slow. However, the rate of homo-coupling can be accelerated by the presence of air, oxygen or redox agents such as Cu(II).<sup>66</sup> Similarly, Stille homo-coupling products can be obtained by using Pd(II) as a catalyst and Cu(II) as co-oxidant.<sup>161</sup>

Consequently, in reviewing the conditions used in the synthesis of boscalid, the homo-coupling reaction was probably accelerated by Cu(II) which was produced by the oxidation of the CuI promoter by traces of air dissolved in the DMF.

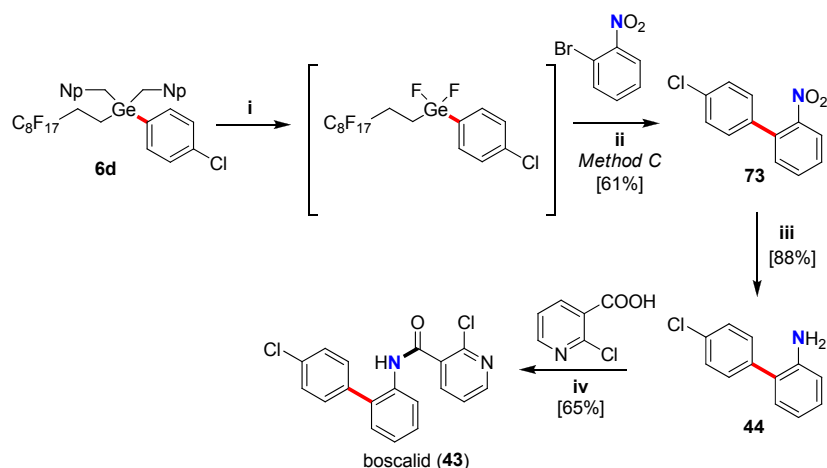
Clearly, the rate of cross-coupling between arylgermane **6d** and the 2-bromo-*N*-trifluoroacetamide **60** is slow. Assuming that the acetamide was possibly responsible for the low rate, a revised approach was drawn up in which 2-bromonitrobenzene was employed as the coupling partner (Scheme 2.6.32).



**Scheme 2.6.32.** Final disconnection for boscalid.

4-Chloro-2'-nitrobiphenyl **73** was synthesised in 61 % yield under the optimised photolysis/cross-coupling conditions. Examination of the crude biphenyl products revealed that no homo-coupling product **72** was detectable. It is noteworthy that the relatively sterically hindered aryl bromide coupled well in this case.

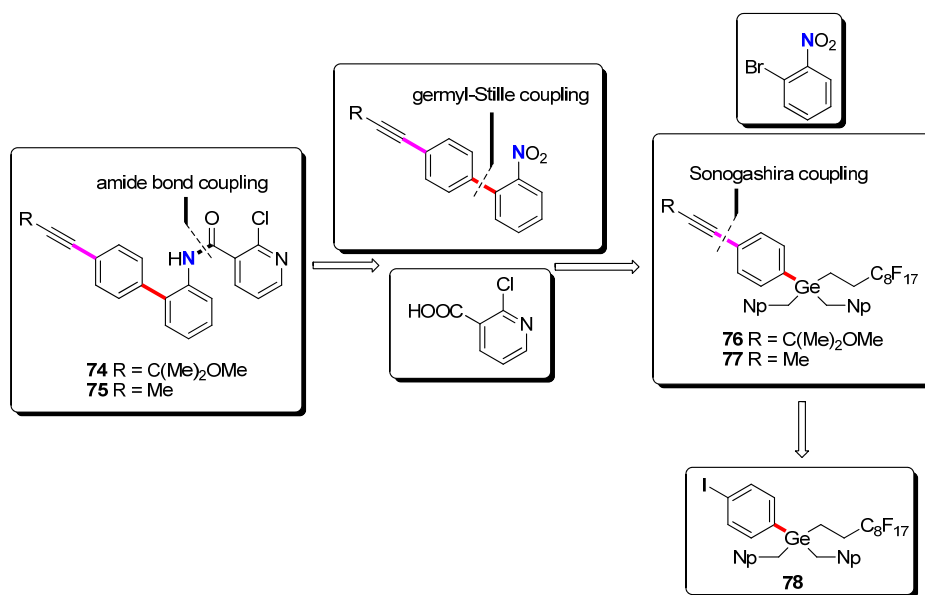
Reduction was achieved by  $SnCl_2$  to give the corresponding 4-chloro-2'-aminobiphenyl **44** in 88 % yield. DCC coupling was then employed to form the amide bond between 4-chloro-2'-aminobiphenyl **44** and 2-chloro-3-nicotinic acid to furnish the target molecule boscalid (**43**) in 65 % yield (Scheme 2.6.33).<sup>162</sup>



**Scheme 2.6.33.** The synthesis of boscalid (**43**).<sup>162</sup>

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$  (4+4 eq.), Pyrex tube, argon purged,  $h\nu$ ,  $\text{MeOH} : \text{MeCN} = 1:3$ , 2 h; ii) *Method C*:  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%),  $\text{P}(2\text{-Tol})_3$  (15 mol%),  $\text{CuI}$ , TBAF, DMF,  $120^\circ\text{C}$ , 16 h.; iii)  $\text{SnCl}_2$ , conc.  $\text{HCl}$ ,  $\text{EtOH}/\text{THF}$ , RT, 16 h; iv) DCC, *cat.* DMAP,  $\text{CH}_2\text{Cl}_2$ , RT, 16 h.

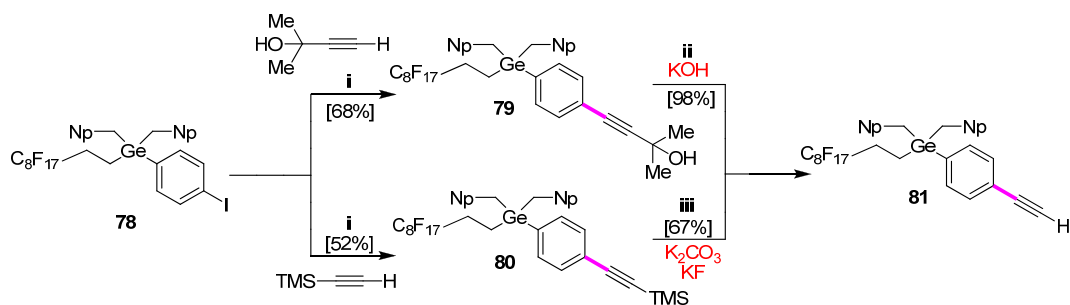
Since this successful approach to boscalid (**43**) no longer required our arylgermane to survive any synthetic steps prior to photolytic activation/cross-coupling, we decided to demonstrate the compatibility of the fluorinated-tagged arylgermanes with synthetic manipulations prior to cross-coupling by preparing some alkynyl-substituted derivatives of boscalid. 2-Chloro-*N*-[4'-(3-methoxy-3-methylbut-1-ynyl)-biphenyl-2-yl]nicotinamide (**74a**) and 2-chloro-*N*-(4'-prop-1-ynylbiphenyl-2-yl)-nicotinamide (**74b**), which contain alkynyl substituents in place of the chloro substituent found in boscalid, have been described in a Syngenta patent<sup>162</sup> as being 'second generation' boscalid-type fungicides. It was planned to employ Sonogashira coupling in the preparation of these compounds (Scheme 2.6.34).<sup>135</sup>



**Scheme 2.6.34.** Proposed disconnection for alkynyl boscalid derivatives **74** and **75**.

The plan was to introduce the phase-tagged cross-coupling partner early in the synthetic route, exploit the phase-tag to enable facile purification of intermediates, and then activate and cross-couple to furnish the desired molecule.

To manifest this idea, two Sonogashira reactions were carried out between fluororous-tagged 4-iodoarylgermane **78** and 2-methylbut-3-yn-2-ol (**78**→**79**, 68%) and ethynyltrimethylsilane (**78**→**80**, 52%) catalysed by Cu(I) and Pd(0).<sup>163</sup> The success of these transformations verified that arylgermanes are orthogonal to Pd-catalysed coupling conditions prior to photoactivation as we expected. Deprotection of the 2-hydroxypropyl group by KOH (**79**→**81**, 98 %) and deprotection of the TMS group (by fluoridolysis, **80**→**81**, 67 %), yielded a common ethynylarylgermane **81**. The success of these transformations demonstrated the orthogonality of the arylgermanes towards fluoridolysis and basic conditions, again as expected (Scheme 2.6.35).

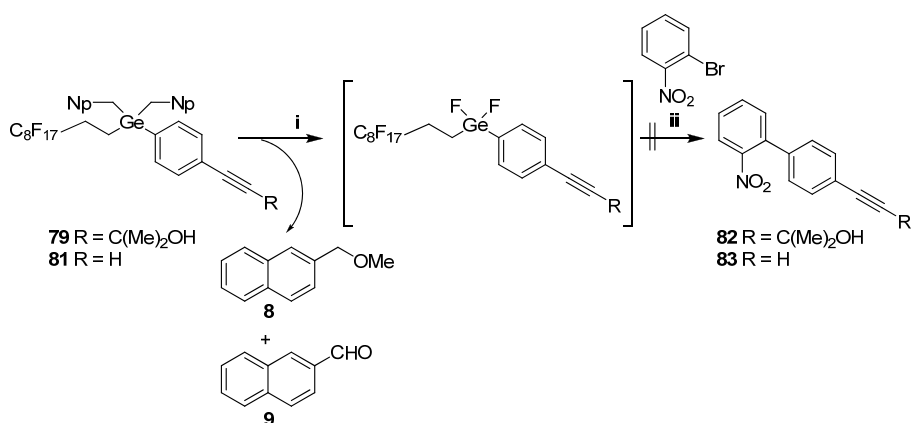


**Scheme 2.6.35.** Sonogashira/germyl-Stille coupling of unmasked alkynes.

*Reagents and conditions:* i) alkynes, Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, CuI, *t*BuNH<sub>2</sub>; ii) *Method D*: KOH, 80 °C; iii)

*Method E*: K<sub>2</sub>CO<sub>3</sub>, KF.

However, neither 3-methyl-3-hydroxybutynylarylgermane **79** nor ethynylarylgermane **81** participated in photolysis/cross-coupling with 2-bromonitrobenzene; no desired biphenyls **82** and **83** could be found, although the key by-products of photolysis **8** and **9** were identified by GC/MS in both cases (Scheme 2.6.36).

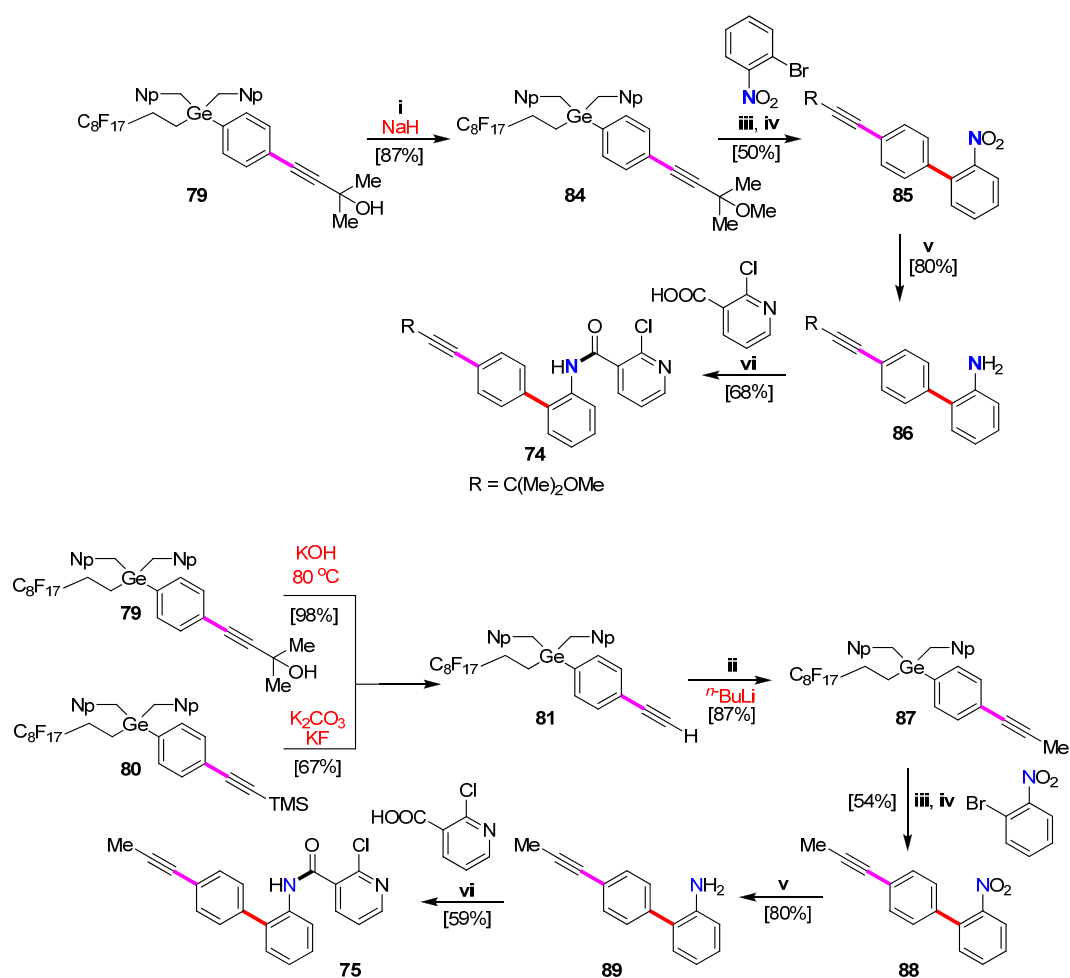


**Scheme 2.6.36.** Attempted to achieve germynl-Stille coupling of alkyne-containing alkynyl arylgermanes **79** and **81**.

*Reagents and conditions:* i) Cu(BF<sub>4</sub>)<sub>2</sub> (4+4 eq.), Pyrex tube, argon purged, hν, MeOH : MeCN = 1:3, 2 h; ii) *Method C*: PdCl<sub>2</sub>(MeCN)<sub>2</sub> (10 mol%), P(2-Tol)<sub>3</sub> (15 mol%), CuI, TBAF, DMF, 120 °C, 16 h.

The unsuccessful cross-coupling of these two substrates may reflect instability of their alkynyl functionalities under the catalytic conditions. In particular, ethynylarylgermane **81** could be generated *in situ* by basic pyrolysis of 3-methyl-3-hydroxybutynylarylgermane **79** in the presence of a nucleophile (e.g. TBAF at 120 °C, *Method C* conditions). To circumvent these issues, methylation of compounds **79** and **81** was carried out using NaH-Me<sub>2</sub>SO<sub>4</sub> (**79**→**84**, 87 % yield)<sup>164</sup> and *n*BuLi/MeOTf (**81**→**87**, 87 % yield)<sup>165,166</sup> to give the desired

alkynylarylgermanes **84** and **87**, respectively. These two alkynylarylgermanes were then subjected to photolysis/cross-coupling with 2-bromonitrobenzene under standard conditions to give the desired biphenyls **85** and **88** in 50 % and 54 % yield, respectively. The biphenyls **85** and **88** were reduced by  $\text{SnCl}_2$  to give 4-(3-methyl-3-methoxybutynyl)-2'-aminobiphenyl **86** in 80 % yield and 4-propynyl-2'-aminobiphenyl **89** in 80 % yield. Finally, DCC coupling with 2-chloro-3-nicotinic acid gave alkynyl boscalid analogues, 2-chloro-*N*-[4'-(3-methoxy-3-methylbut-1-ynyl)biphenyl-2-yl]nicotinamide (**74**, 68 % yield) and 2-chloro-*N*-(4'-prop-1-ynylbiphenyl-2-yl)nicotinamide (**75**, 59 % yield) (Scheme 2.6.37).



**Scheme 2.6.37.** Synthesis pathways for alkynyl analogues of boscalid **74** and **75**.<sup>162</sup>

*Reagents and conditions:* i)  $\text{NaH}$ ,  $\text{Me}_2\text{SO}_4$ , THF; ii)  $n\text{-BuLi}$ , DMPU,  $\text{MeOTf}$ , THF,  $-78\text{ }^\circ\text{C}$ ; iii)

$\text{Cu}(\text{BF}_4)_2$  (4+4 eq.), Pyrex tube, argon purged,  $h\nu$ ,  $\text{MeOH} : \text{MeCN} = 1:3$ , 2 h; iv) *Method C*:

2-bromo-nitrobenzene,  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%),  $\text{P}(2\text{-Tol})_3$  (15 mol%),  $\text{CuI}$ , TBAF, DMF,  $120\text{ }^\circ\text{C}$ ,

16 h; v)  $\text{SnCl}_2$ , conc.  $\text{HCl}$ ,  $\text{EtOH/THF}$ , RT, 16 h; vi) DCC, *cat.* DMAP,  $\text{CH}_2\text{Cl}_2$ , RT, 16 h.

The stability of the *R*<sub>f</sub>-tagged arylgermanes towards the various reaction conditions employed during the synthesis of the above boscalid analogues, such as the NaH and <sup>n</sup>BuLi used for the methylation of compound **79** and **81**, and the fluoridolysis and basic pyrolysis procedures used for the formation of compound **81**, reveal remarkable tolerance of these compounds towards reaction conditions of routine use in synthesis. Moreover, this methodology displays high performance in both linear and parallel synthetic design for rapidly diversifying target molecules whilst benefiting from facile purification by F-SPE.

Precedent in the literature for the concept demonstrated above is relatively rare. There is an emerging body of work from the Molander labs relating to the use of aryl and alkenyl trifluoroborate salts as robust precursors for Suzuki coupling.<sup>167</sup> However, purification of these trifluoroborate salts and their intermediates prior to cross-coupling can only be achieved by means of crystallisation which is unsuitable for micro-scale use. More recently, Burke has shown that *N*-methyliminodiacetic acid (MIDA) boronate-based coupling partners can be used in multistep synthesis.<sup>168,169</sup> Upon treatment of MIDA-boronates with aqueous basic conditions (NaOH<sub>(aq)</sub>/THF or NaHCO<sub>3(aq)</sub>/MeOH, RT), the corresponding boronic acids are liberated for cross-coupling with electrophiles. However, the MIDA-boronate-based coupling substrates are less stable to strong nucleophiles (*e.g.* LiAlH<sub>4</sub>, TBAF and metal alkoxides as compared to arylgermanes, *cf.* Table 2.6.5). Nevertheless, the MIDA-tagged boronates have proved very useful for the synthesis of bioactive products.<sup>169</sup>

#### 2.6.4. Conclusions

The scope of the sequential germyl-Stille photoactivation/cross-coupling reaction has been investigated under optimised photolysis and cross-coupling conditions. Coupling yields are strongly affected by the electronic nature of both the nucleophilic and the electrophilic aryl partners. Electron-rich arylgermanes cross-couple particularly well with electron-deficient aryl bromides. In addition, the stability profile of an *R*<sub>f</sub>-tagged phenylgermane has been delineated. The tolerance of the arylgermane unit towards strongly basic and nucleophilic conditions for extended periods of time is good.

The key biaryl agrochemical boscalid **43** and two of its analogues have been synthesised using the germyl-Stille cross-coupling reaction. The successful approach developed differs from the original synthetic route envisaged because amine and acetamide groups on the *R<sub>f</sub>*-tagged arylgermane were found to be unsuitable for the photolysis/cross-coupling reactions. The synthetic routes to boscalid analogues 2-chloro-*N*-[4'-(3-methoxy-3-methylbut-1-ynyl)biphenyl-2-yl]nicotinamide (**74**) and 2-chloro-*N*-(4'-prop-1-ynylbiphenyl-2-yl)nicotinamide (**75**) demonstrate that the fluororous-tagged arylgermanes can survive various chemical manipulations including Sonogashira coupling and butyllithium treatment. This underscores the concept of iterative chemical manipulation of the *R<sub>f</sub>*-tagged arylgermanes prior to activation and coupling: the arylgermane coupling precursors are chemically stable, easy to handle and readily purified.

#### **2.6.5 Development of alkenyl germyl-Stille cross-coupling reactions for stereocontrolled styrene synthesis**

Pd-catalysed cross-coupling of alkenyl organosilanes and organostannanes have been used for the alkenylation of wide ranges of aromatics and to effect macrocyclisation during natural product synthesis.<sup>57</sup> Alkenyl organometallics are generally of higher reactivity as compared to the corresponding aryl congeners with respect to transmetalation with  $\text{Ar}^2\text{Pd}^{\text{II}}\text{XL}$  complexes. However, as well as directly undergoing transmetalation with  $\text{Ar}^2\text{Pd}(\text{II})$  complexes to give *ipso* cross-coupling products, alkenyl organometallics can also undergo electrophilic carbopalladation under certain circumstances resulting in stereo- and regioisomeric mixtures.

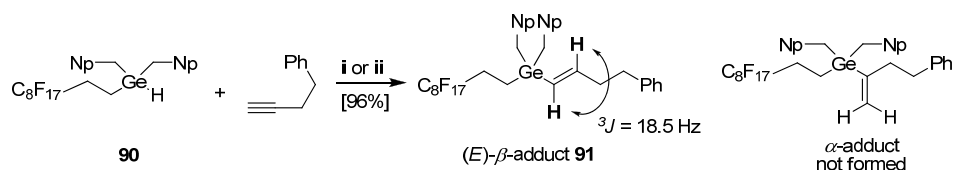
Following our successful demonstration of the utility of aryl-aryl germyl-Stille coupling reactions for the synthesis of boscalid and analogues, our attention was focused on alkenyl-aryl cross-coupling using alkenyl germanes as coupling substrates. The initial reaction parameters for this protocol were those optimised conditions employed for aryl-aryl germyl-Stille coupling reactions.

### 2.6.5.1 Synthesis of R<sup>f</sup>-tagged (*E*)-alkenyl germanes via hydrogermylation

Alkenyl group 14 metal reagents are magnificent tools for derivatisation of molecules by transition metal-catalysed cross-coupling reactions or by *ipso*-electrophilic demetallation to furnish alkenyl-substituted products. Efficient regio- and stereocontrolled synthesis of the alkenylmetal reagents can usually be achieved by hydrometalation of alkynes.<sup>170</sup>

Hydrostannation and hydrosilylation of terminal alkynes are well documented for the preparation of alkenyl stannanes and silanes for Pd-catalysed cross-coupling reactions. This transformation can be achieved by radical initiated addition of hydrostannanes (or hydrosilanes) to alkynes, by analogous transition metal catalysed processes (*e.g.* using Pd, Rh and Pt complexes), or thermally. Regio- and stereoselectivity can be most easily controlled for the metal catalysed cases by the means of carefully controlling the ligands and conditions of the reaction.<sup>171,172</sup> Similarly, alkenylgermanes can be prepared by hydrogermylation of germanium hydrides with terminal alkynes facilitated by Pd,<sup>173</sup> Pt<sup>174</sup> or Rh complexes<sup>175-177</sup> or by Lewis acids under mild reaction conditions.

R<sup>f</sup>-tagged alkenylgermane **91** was chosen as a model molecule to explore sequential photoactivation/cross-coupling. Following a procedure reported by Wada, upon treatment germane hydride **90** with 4-phenylbutyne in the presence of RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub> as a catalyst, (*E*)-alkenylgermane **91** was obtained in 96 % yield (Scheme 2.6.38).<sup>175</sup>



**Scheme 2.6.38.** Synthesis of R<sup>f</sup>-tagged (*E*)-alkenyl germane **91** by hydrogermylation.

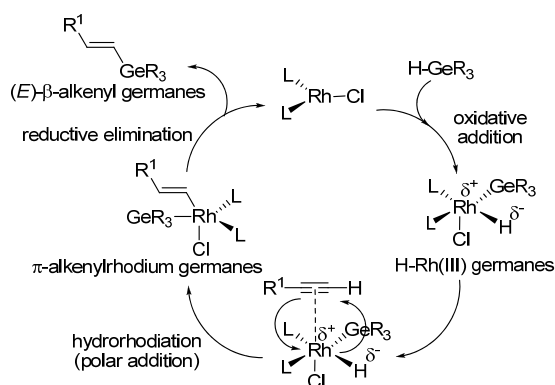
*Reagents and conditions:* i) RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub>, galvinoxyl, CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 24 h; ii) RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 24 h.

The stereochemistry of the alkene was confirmed by the characteristic *J* = 18.5 Hz vicinal coupling constant between the *trans* alkene protons.

Wada reported that hydrogermylation of tributylgermanium hydride with phenylacetylene catalysed by the  $\text{RhCl}(\text{CO})(\text{PPh}_3)_2$  complex gave good regioselectivity for  $\beta$ -adducts (93 % vs. 7 %  $\alpha$ -adducts) but with moderate stereoselectivity ( $E : Z = 70 : 23$ ).<sup>175</sup> With radical inhibitor galvinoxyl as an additive, Wada found that the regio- and stereoselectivity of the (*E*)- $\beta$ -adduct was improved (99 % of  $\beta$ -adduct with  $E : Z = 91 : 8$ ).<sup>175</sup> For our reaction, the (*E*) stereochemistry of the exclusive product alkenyl germane **91** was verified by a large vicinal coupling constant with  $^3J = 18.5$  Hz in its  $^1\text{H}$  NMR spectrum. However, the desired product could not be separated as a pure substance from galvinoxyl-derived contaminants.

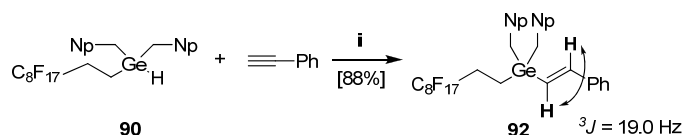
Fortunately, identical regio- and stereoselectivity were observed when the hydrogermylation was carried out in the absence of galvinoxyl but otherwise identical conditions. (*E*)-Alkenyl germane **91** was formed exclusively in 96 % yield. The high regio- and stereoselectivities probably reflect suppression of the  $\alpha$ -adduct by virtue of the steric hindrance provided by the bulky bis(2-naphthylmethyl) groups on the germanium hydride **90**.

The regio- and stereoselectivity of hydrometallation reactions mediated by transition-metals are influenced by the metal-complex employed, the source of the metal hydride and the other parameters. Nevertheless, a catalytic pathway of hydrogermylation mediated by a Rh(I)-complex was proposed by Esterulas.<sup>176</sup> Trialkylgermanium hydride was proposed to undergo oxidative addition with the Rh(I) complex to afford a H-Rh(III) germane intermediate in which the polarised H-Rh bond undergoes facile hydorrhodiation of the alkyne *via* polar addition. The polar addition step is the regiochemistry determining step and exhibits strong dependence on the substrate and Rh-complex. The resulting  $\pi$ -alkenylrhodium germane intermediate then undergoes reductive elimination to furnish the desired alkenyl germane and the regenerate Rh(I)-complex (Scheme 2.6.39).<sup>176</sup>



**Scheme 2.6.39.** Esterulas' proposed mechanism of Rh-catalysed hydrogermylation of alkynes to afford (*E*)-β-alkenyl germanes.<sup>176</sup>

(*E*)-Styrenyl germane **92** was also prepared by hydrogermylation in the absence of galvinoxyl (Scheme 2.6.40).



**Scheme 2.6.40.** Synthesis of *R<sub>f</sub>*-tagged (*E*)-alkenyl germane **92** by hydrogermylation.

*Reagents and conditions:* i) RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 24 h.

Highly stereoselective (*E*)-β-alkenyl germane formation was observed, the stereochemistry again being confirmed by the characteristic  $J = 19.0$  Hz vicinal coupling constant between the *trans* alkene protons.

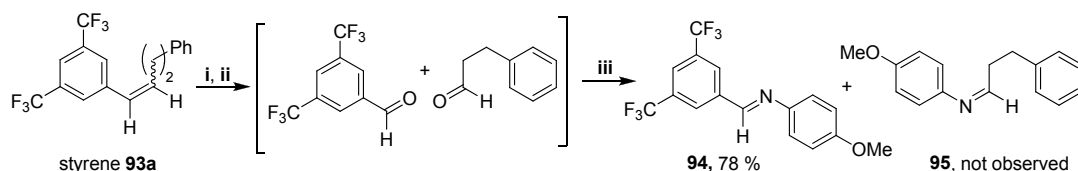
### 2.6.5.2 Exploring the scope and selectivity of alkenyl germyl-Stille cross-coupling

(*E*)-alkenyl germane **91** was subjected to photolysis using the previously optimised protocol. As before, three signals at *ca.* -164 ppm were apparent in the <sup>19</sup>F NMR spectrum of the intermediate coincident with the conclusion of the photolysis of period. It was therefore assumed that as in the arylgermane cases, a dimer and a monomer of the difluoro alkenyl germane had been formed and that these co-existed in the solution. That this situation mirrors closely that found for the arylgermanes suggests that the F↔F interactions may be dominant in dictating the formation of the head-to-head topology of the dimer rather than π-π interactions. Based on the vicinal

coupling constant ( $^3J = 18.5$  Hz) of the alkenyl subunit the  $^1\text{H}$  NMR spectrum of this alkenyl difluorogermane, no photoinduced isomerisation occurred during this photoactivation process. Thus, the (*E*)-alkenyl difluoro germane intermediate was submitted to the sequential cross-coupling reaction without further purification.

Coupling with 3,5-bis(trifluoromethyl)bromobenzene afforded a coupling product **93a** in 65 % yield. Its  $^1\text{H}$  NMR spectrum exhibited vicinal coupling pattern which could not be readily reconciled with (*E*)- $\beta$ -styrene geometry due to second order distortion resulting from the two protons being close in chemical shift. Two alternative possible structural assignments were considered: an  $\alpha$ -substituted or a (*Z*)-configured  $\beta$ -styrene.

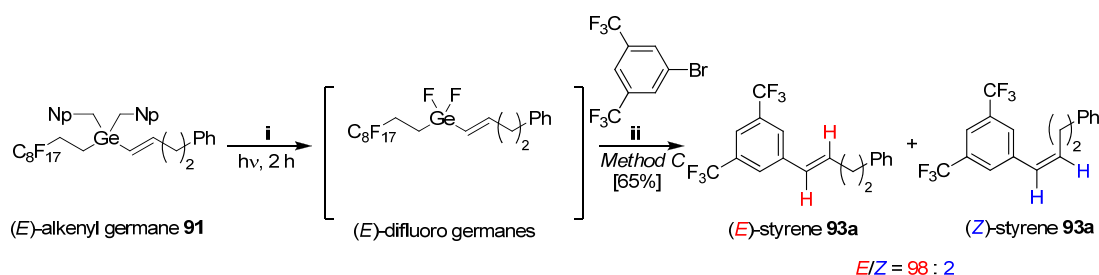
In order to determine the regiochemistry of this product, ozonolysis of the styrene followed by reductive cleavage of the resulting ozonides was undertaken with *in situ* reaction with 4-anisidine. Imine **94** was isolated in 78 % yield but the other fragment was not detected. The formation of imine **94** excluded the possibility of the product being an  $\alpha$ -substituted styrene. Therefore, the product of the reaction was concluded to be either the expected (*E*)- $\beta$ -styrene or the (*Z*)- $\beta$ -styrene **93a** (Scheme 2.6.41).



**Scheme 2.6.41.** Ozonolysis/reductive cleavage then imine formation on styrene **93a**-proof of regiochemistry.

*Reagents and conditions:* i)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 15 min; ii)  $\text{PPh}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C} - \text{rt}$ , 1 h; iii) 4-anisidine,  $\text{CH}_2\text{Cl}_2$ , 2 h.

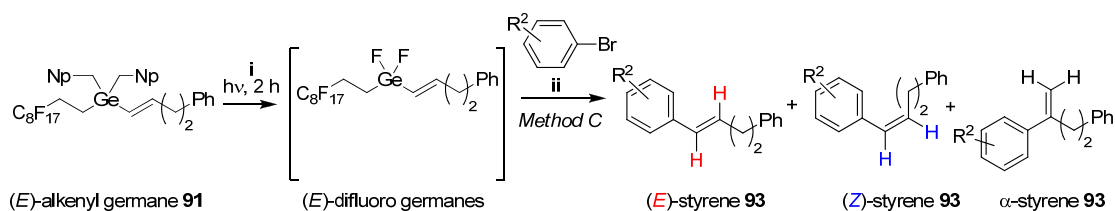
1D and 2D  $^1\text{H}$  NMR experiments could not unambiguously distinguish these two possibilities either. GC-MS analysis revealed the ratio of isomers to be 98 : 2 (Scheme 2.6.42). Eventually, the major isomer of this reaction was proven to be the expected (*E*)- $\beta$ -styrene by a 4<sup>th</sup> year project student in the group (Mungyuen Li, Spivey group, 2008-2009). He prepared authentic samples of the *E* and *Z* configured alkenes **93c** (see Table 2.6.9) which displayed the same ambiguous NMR feature.<sup>178</sup>



**Scheme 2.6.42.** Alkenyl germyl-Stille cross-coupling with 3,5-bis(trifluoromethyl)bromobenzene affording (*E*)-styrene **93a**.

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$ , Pyrex tube, argon purged, hv,  $\text{MeOH} : \text{MeCN} = 1:3$ , ii) *Method C*:  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%),  $\text{P}(2\text{-Tol})_3$  (15 mol%), TBAF, CuI, DMF, 120 °C, 16 h.

(*E*)-Alkenyl germane **91** was next employed as a substrate for cross-coupling with a series of aryl bromides varying in electronic nature. All the resulting crude product mixtures were examined by the means of  $^1\text{H}$  NMR and GC-MS analysis for the determination of isomer ratios (Table 2.6.9).



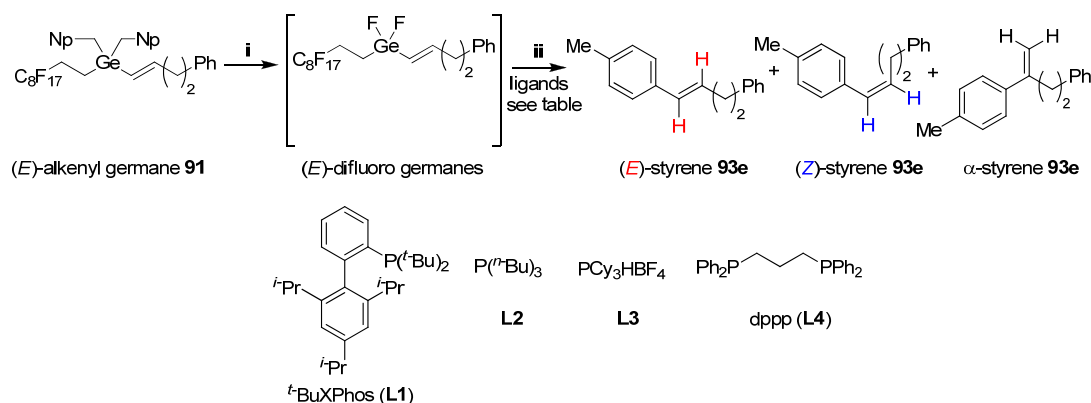
| Entry | $\text{R}^2$                          | Product    | Yield<br>(%) | Isomer ratio                               |
|-------|---------------------------------------|------------|--------------|--------------------------------------------|
|       |                                       |            |              | ( <i>E</i> )- : ( <i>Z</i> )- : $\alpha$ - |
| 1     | 3,5-bis( $\text{CF}_3$ ) <sup>a</sup> | <b>93a</b> | 65           | 98 : 2 : 0                                 |
| 2     | 4-CN <sup>a</sup>                     | <b>93b</b> | 65           | 99 : 1 : 0                                 |
| 3     | 4-Ac <sup>a</sup>                     | <b>93c</b> | 59           | 100 : 0 : 0                                |
| 4     | 3,5-di( $\text{CH}_3$ )               | <b>93d</b> | 63           | 93 : 5 : 2                                 |
| 5     | 4-Me                                  | <b>93e</b> | 72           | 80 : 8 : 12                                |
| 6     | 4-OMe                                 | <b>93f</b> | 40           | 67 : 13 : 20                               |
| 7     | 4-Cl                                  | <b>93g</b> | 52           | 73 : 1 : 26                                |
| 8     | 4-F                                   | <b>93h</b> | 58           | 93 : 2 : 5                                 |
| 9     | 2- $\text{NO}_2$                      | <b>93i</b> | 48           | 80 : 20 : 0                                |

<sup>a</sup> The  $^1\text{H}$  NMR spectra of these compounds are difficult to assign due to second order effects resulting from the vicinal alkenyl protons bearing very similar chemical shifts (see Text).

**Table 2.6.9.** Germyl-Stille cross-coupling of (*E*)-alkenyl germane **91** with various aryl bromides.

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$ , Pyrex tube, argon purged, hv,  $\text{MeOH} : \text{MeCN} = 1:3$ , ii) *Method C*:  $\text{PdCl}_2(\text{MeCN})_2$  (10 mol%),  $\text{P}(2\text{-Tol})_3$  (15 mol%), TBAF, CuI, DMF, 120 °C, 16 h

It can be seen that the expected (*E*)-alkenes are produced in all cases. Although styrenes were obtained with high (*E*)-selectivity by coupling with electron-deficient aryl bromides, the selectivity achieved by coupling with electron-rich substrates was unsatisfactory. Since we were keen to develop a method that would provide styrenes of (*E*)-configurations with high selectivity optimisation studies were carried out using alkenyl germane **91** and 4-bromotoluene. Various supporting ligands were screened for their effects on this reaction (Table 2.6.10).



| Entry | L                     | Yield<br>(%) | Isomer ratio<br>( <i>E</i> )- : ( <i>Z</i> )- : $\alpha$ - |
|-------|-----------------------|--------------|------------------------------------------------------------|
| 1     | <b>L1</b>             | 65           | <b>94</b> : <b>5</b> : 1                                   |
| 2     | <b>L2</b>             | 62           | <b>98</b> : <b>1</b> : 1                                   |
| 3     | <b>L3<sup>a</sup></b> | 71           | <b>100</b> : <b>trace</b> : trace                          |
| 4     | <b>L4</b>             | 42           | <b>100</b> : <b>trace</b> : trace                          |

<sup>a</sup> addition of  $t\text{-Pr}_2\text{NEt}$  (15 %mol)

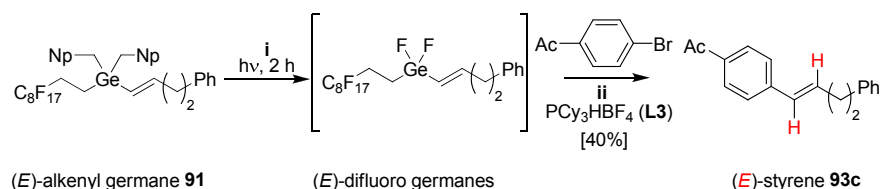
**Table 2.6.10.** Screening of phosphine ligands to effect (*E*)-stereoselective styrene formation

*Reagents and conditions:* i)  $\text{Cu}(\text{BF}_4)_2$ , Pyrex tube, argon purged,  $h\nu$ ,  $\text{MeOH} : \text{MeCN} = 1:3$ , ii)

$\text{PdCl}_2(\text{MeCN})_2$  (10 mol%), ligands (15 mol%), TBAF,  $\text{CuI}$ , DMF,  $120^\circ\text{C}$ , 16 h.

Gratifyingly, all the ligands screened gave improved (*E*)-selectivity in this reaction as compared to the original conditions using  $\text{P}(2\text{-Tol})_3$  as a ligand (*cf.* Table 2.6.38, entry 5). Sterically hindered electron-rich ligand  $t\text{-BuXPhos}$  (**L1**) and  $\text{P}(t\text{-Bu})_3$  (**L2**) both gave high levels of (*E*)-selectivity (entries 1 and 2). Superior (*E*)-selectivity still was obtained by employing  $\text{PCy}_3 \cdot \text{HBF}_4$  (**L3**) and dppp (**L4**) as ligands (entries 3 and 4). However, an inferior coupling yield (42 %) resulted when using the dppp ligand and so  $\text{PCy}_3 \cdot \text{HBF}_4$  (**L3**) is the preferred ligand for mediating (*E*)-styrene formation with good reaction yields when cross-coupling with electron-rich aryl bromides.

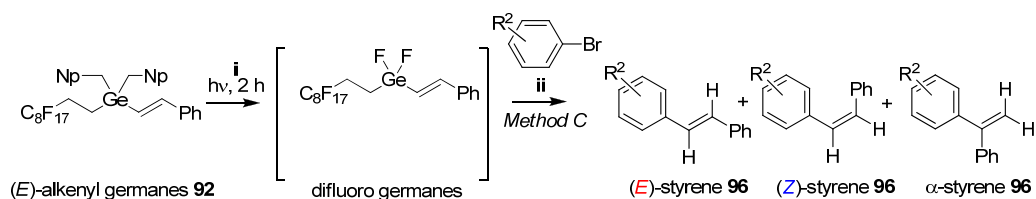
Cross-coupling of (*E*)-alkenyl germane **91** with electron-deficient 4-bromoacetophenone using PCy<sub>3</sub> · HBF<sub>4</sub> (**L3**) as a ligand still gave the high (*E*)-selectivity as observed previously albeit in a poor reaction yield (Scheme 2.6.43).



**Scheme 2.6.43.** Use of PCy<sub>3</sub> · HBF<sub>4</sub> ligand in (*E*)-selective cross-coupling with germane **91**.

*Reagents and conditions:* i) Cu(BF<sub>4</sub>)<sub>2</sub> (2 x 4eq.), Pyrex tube, argon purged, hv, 2 h, MeOH : MeCN = 1:3, ii) PdCl<sub>2</sub>(MeCN)<sub>2</sub> (10 mol%), PCy<sub>3</sub>HBF<sub>4</sub> (15 mol%), <sup>t</sup>Pr<sub>2</sub>NEt (15 %mol), TBAF, CuI, DMF, 120 °C, 16 h.

In order to see how general the above trends were, the (*E*)-styrenyl germane **92** was investigated for cross-coupling with selected aryl bromides (Table 2.6.11).



| Entry | R <sup>2</sup>            | Product    | Yield<br>(%) | Isomer ratio<br>( <i>E</i> )- : ( <i>Z</i> )- : α- |
|-------|---------------------------|------------|--------------|----------------------------------------------------|
| 1     | 3,5-bis(CF <sub>3</sub> ) | <b>96a</b> | 58           | 82 : 17 : 1                                        |
| 2     | 4-CN                      | <b>96b</b> | 60           | 90 : 10 : 0                                        |
| 3     | 4-Ac                      | <b>96c</b> | 66           | 100 : 0 : 0                                        |
| 4     | 4-Me                      | <b>96d</b> | 52           | 99 : 1 : 0                                         |

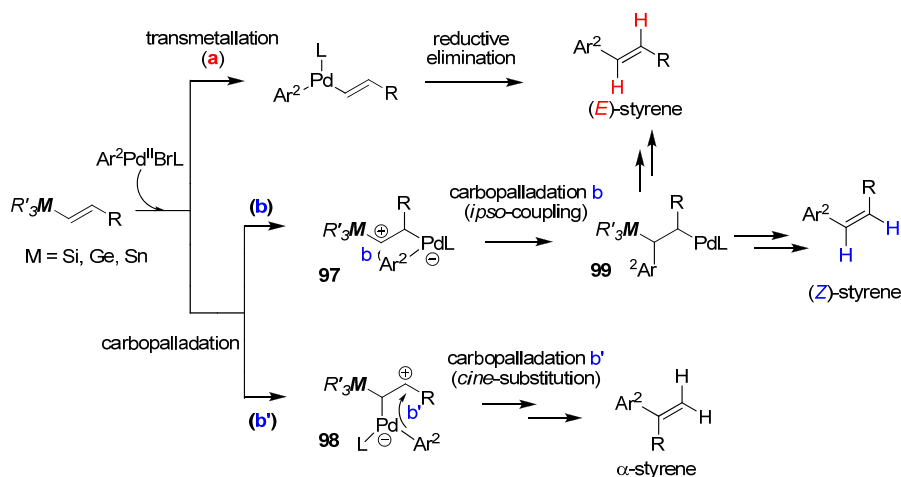
**Table 2.6.11.** Germyl-Stille cross-coupling of alkenyl germanes with aryl bromides.

*Reagents and conditions:* i) Cu(BF<sub>4</sub>)<sub>2</sub>, Pyrex tube, argon purged, hv, MeOH : MeCN = 1:3, ii) *Method C*: PdCl<sub>2</sub>(MeCN)<sub>2</sub> (10 mol%), P(2-Tol)<sub>3</sub> (15 mol%), TBAF, CuI, DMF, 120 °C, 16 h

A similar stereoselectivity profile was found when coupling styrenyl germane **92** with aryl bromides. For this substrate too, (*E*)-stilbenes were obtained as the major stereoisomers irrespective of the electronic demand of the aryl bromide partners (entries 1-4).

The presence of various isomers during the Pd-catalysed cross-coupling of (*E*)-alkenyl germanes with aryl bromides undoubtedly reflects the fact that there are

(at least) two mechanistically distinct pathways by which coupling can occur in alkenyl group 14 metal cross-coupling reactions: (a) a direct transmetallation route as proposed for the aryl-aryl coupling (*i.e.* germyl-Stille coupling) leading to (*E*)- $\beta$ -styrenes; and (b) a regioselective carbopalladation route (*i.e.* Heck reaction) followed by nucleophile-assisted elimination of the germane moiety and Pd(0) affording  $\alpha$  (*cine*) and/or  $\beta$  (*ipso*) styrenes (Scheme 2.6.44).



**Scheme 2.6.44.** Proposed reaction pathways for alkenyl group 14 metal cross-coupling reactions.

In general, cross-coupling of alkenylsilanes and alkenylstannanes with aryl (pseudo)halides are highly selective and to furnish coupled products with retention of the regio- and stereochemistry of the alkenylmetals employed [*i.e.* (*E*)-substrates  $\rightarrow$  (*E*)-products; (*Z*)-substrates  $\rightarrow$  (*Z*)-products]. The high selectivity is attributed to rapid transmetalation with the  $Ar^2Pd^{II}$  complex (route a) followed by reductive elimination.<sup>96</sup> However, some instances in which coupling of (*Z*)- or  $\alpha$ -substituted alkenylmetals with aryl (pseudo)halides gave thermodynamically favoured (*E*)-alkene products have been reported.<sup>179,180</sup> These cases proceed *via* carbopalladation (route b) presumably because the transmetalation pathway is relatively slow. Kikukawa's cross-coupling of alkenyl germanes with arenediazonium salts discussed earlier (Table 2.3.1) is a case in point.<sup>117</sup> To suppress the carbopalladation route, Corey found that addition of Cu(I) salts can effectively accelerate route a by pre-transmetalation to give an alkenylcopper intermediate which then undergoes rapid transmetalation with the  $Ar^2Pd^{II}$  complex.<sup>179</sup>

Although the formation of (*E*)-alkenes from (*Z*)- or  $\alpha$ -substituted substrates has been well documented,<sup>180-183</sup> formation of (*Z*)-alkenes from (*E*)-coupling partners is rare in

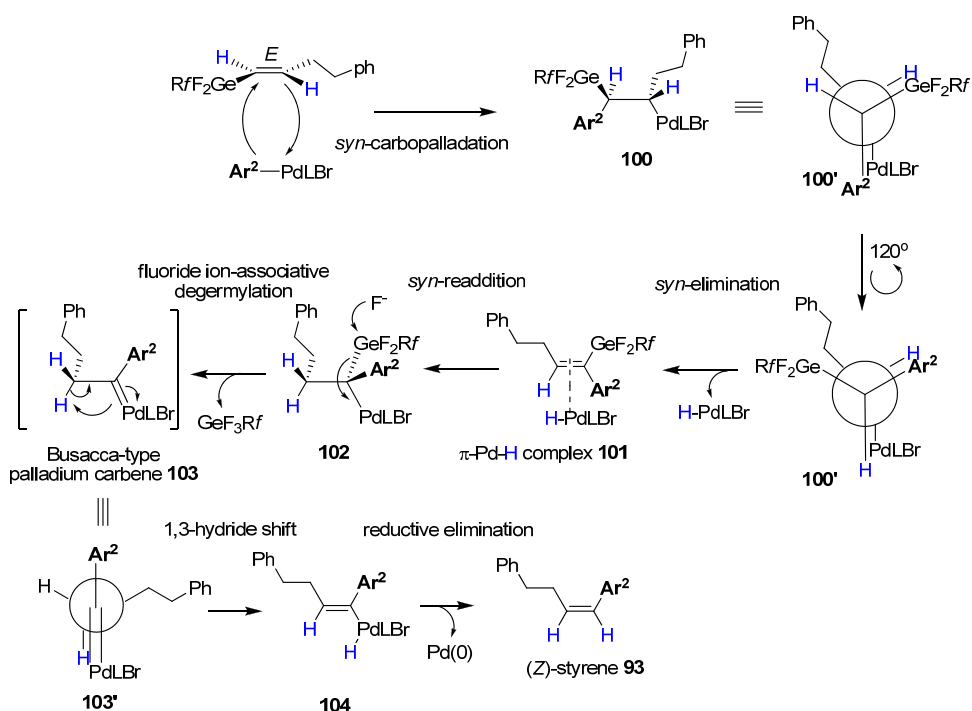
the literature. An example has been reported by Blart who found that cross-coupling of an (*E*)-alkenylsilane with 4-anisyl iodide gave a mixture of styrenes in 80 % yield in which (*Z*)- and  $\alpha$ -substituted products were identified as being present in the same ratio.<sup>184</sup>

Divergence between the two coupling pathways, at least for alkenylsilanes and stannanes, has been suggested to be influenced by the reactivity of the particular alkenyl metal reagent and the catalyst system employed.<sup>185</sup> The transmetalation pathway usually predominates when the alkenyl metal is comprised of an alkene bearing a non-hindered group at the  $\beta$ -position that can readily migrate. Hence, the transmetalation process would be expected to proceed rapidly in the case of both the alkenyl germane **91** and the styrenyl germane **92**. Consequently, (*E*)-stilbenes are the major products in all cases.

The experimental results suggest that the carbopalladation route does however operate to a limited degree in several cases. Two orientations for addition of the  $\text{Ar}^2\text{Pd}^{\text{II}}\text{BrL}$  complex to the difluoroalkenyl germanes are possible. Regioselective formation of intermediate **97** (*via* route b) or **98** (*via* route b') is likely to be influenced by steric and electronic factors.<sup>186</sup>

Although the carbocation  $\beta$  to the Ge centre in the intermediate **98** will be stabilised by hyperconjugation from the Ge-C bond ( $\sigma_{\text{C-Ge}} \rightarrow p_{\text{vac}}$ ), the electronegative fluorine atoms on the Ge centre will diminish the stabilisation contributed by this  $\beta$ -effect. As a result, route b' appears to be a disfavoured pathway by which  $\alpha$ -styrenes are formed *via cine*-substitution as minor products when electron-rich substrates are used.<sup>92</sup> This minor carbopalladation route could probably be suppressed by using different ligands.

The regioselective carbopalladation (*via* route b) is a slightly more favourable pathway that affords intermediate **100** leading to  $\beta$ -substituted styrenes as final products (Scheme 2.6.45).



**Scheme 2.6.45.** Proposed mechanism for cross-coupling of (*E*)-alkenyl germanes with electron-deficient aryl bromides to leading (*Z*)-styrenes *via* a Pd-carbene intermediate.

Carbopalladation of the alkenyl germane with the  $\text{Ar}^2\text{Pd}^{\text{II}}\text{BrL}$  complex should proceed in a *syn*-fashion to give intermediate **100**. Facile *syn*-elimination of Pd-H affords a  $\pi$ -Pd-H complex **101** which then re-adds to the alkene yielding intermediate **102**. Subsequent,  $\alpha$ -degermylation facilitated by fluoride ions leads to Busacca-type palladium carbene complex **103** in which the geometry of the styrene is as shown in the projection **103'**.<sup>187</sup> Upon 1,3-hydride shift and reductive elimination of Pd(0), (*Z*)-styrenes **93** are formed.

It is also possible that the (*Z*)-styrene products are formed by directly *syn*-elimination of the germane moiety and Pd(0) from intermediate **100'** but a driving force for this is not apparent. Clearly, further experiments need to be carried out in order to clarify these mechanistic interpretations.

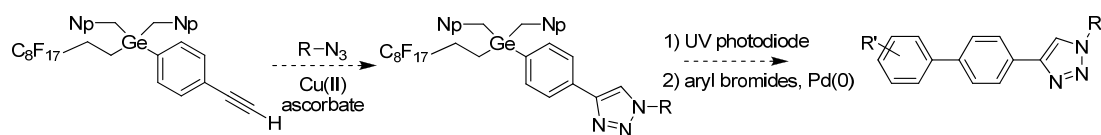
### 2.6.5.3 Conclusion

Rh-catalysed hydrogermylation has been performed to prepare (*E*)-alkenyl germanes with high regio- and stereoselectivity in excellent yields. Photoactivation of these (*E*)-substrates proceeded under the optimised conditions and no photoinduced double-bond isomerisation occurred.

Coupling of the photoactivated (*E*)-alkenyl germanes with aryl bromides in the presence of Pd catalysts resulted in the formation of mixture of isomeric alkene products in which the expected (*E*)-isomers predominated in all cases. Although measurable amounts of (*Z*) and sometimes  $\alpha$  substituted isomers were formed, these could be suppressed by appropriate choice of conditions. Mechanisms that can account for these results have been discussed.

### 2.7 Future work

Although the structures of the photoactivated difluoro germanes have been assigned as a mixture of monomer and dimer co-existing in the system according to  $^{19}\text{F}$  and  $^1\text{H}$  NMR spectroscopic analysis, it is planned to further elucidate their structure by X-ray crystallography. It is also planned to adapt the developed germyl-Stille cross-coupling method for the synthesis of libraries of biaryls by parallel synthesis using UV light delivered to 96 well plate arrays using optical fibres. It is further planned to exemplify this method by using Sharpless click chemistry and germyl-Stille coupling to prepare libraries of bioactive biaryl triazoles (Scheme 2.7.1).<sup>188</sup>



**Scheme 2.7.1.** Proposed approach to biaryl libraries using Sharpless click chemistry/germyl Stille coupling reactions.

It is also intended to carry out mechanistic studies to elucidate the reaction pathway and scope of the cross-coupling of (*E*)-alkenylgermanes with aryl bromides to give styrenes.

### 3. Development of *ipso*-iododegermylation as a method for radio-labelling

#### 3.1 Introduction

##### 3.1.1 Introduction to cannabinoid receptors

Cannabinoid receptors obtained their name as a result of their response to cannabinoid drugs *e.g.*  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) from *Cannabis sativa* (marijuana) and its synthetic analogues. These receptors have been classified as belonging to the rhodospin family of G protein-coupled receptors (GPCRs). Two subtypes of receptors were identified: cannabinoid receptor type 1 (CB1) and type 2 (CB2). The CB1 receptor abounds in the brain and central nervous system (CNS), whereas the CB2 is found mainly in the immune system.<sup>189</sup>

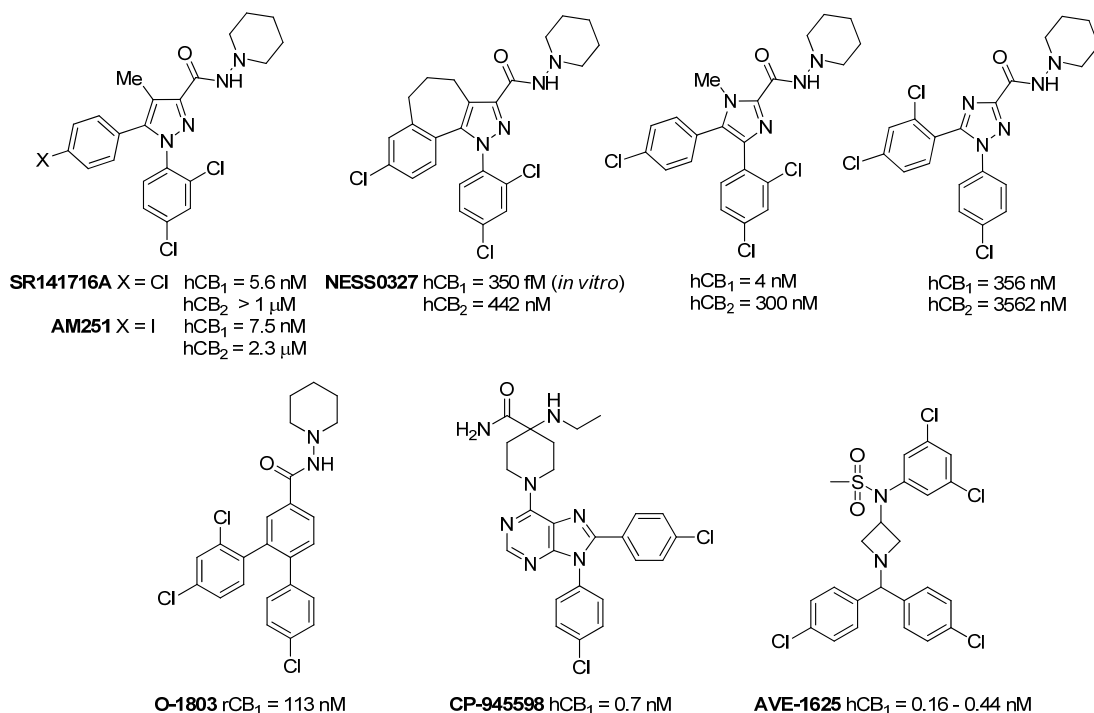
Human CB1 receptors are encoded by an amino sequence of 472 residues deduced by complementary DNA encoding<sup>190</sup> and molecular cloning of the receptor.<sup>191</sup> As for other proteins belonging to the rhodospin family, the receptor has 7 transmembrane helical (TMH) domains of which the TMH-4 and 5 domains are responsible for the high affinity ligand binding site.<sup>192</sup>

Recently studies on the physiological roles of the CB1 receptor disclosed strong correlations with inhibition of adenylyl cyclase, pain control, regulation of ion channels, modulation of energy intake, and various other signal transduction pathways.<sup>193,194</sup> Among these functions, the most promising feature of this receptor's regulatory profile is its role in energy regulation and metabolism. Animal models have revealed that CB1 knock-out mice are leaner than wild-type species.<sup>195</sup> Therefore, blocking the CB1 receptor provides a potential therapeutic strategy for treatment of obesity, metabolic syndrome, drug additions and addiction to smoking.<sup>195</sup>

##### 3.1.2 Antagonists and inverse agonists of CB1 receptors

The Sanofi-Aventis compound **SR141716A**, also known as rimonabant, displays nanomolar inhibition of the CB1 receptor and micromolar inhibition of the CB2 receptor. **SR141716A** is a diarylpyrazole-based ligand which was the first efficient

competitive antagonist for selective blocking of the CB1 receptors. It was discovered in 1994.<sup>196</sup> An analogue, **AM251**, which has an iodine-substituent in place of a chlorine atom in the 5-phenyl ring of rimonabant, has similar inhibitory activity and selectivity for CB1 whilst also providing an opportunity to introduce a radio-iodine isotope to allow visualisation of the CNS by PET or SPECT.<sup>193,194</sup> Although ring-constrained analogue **NESS0327** has been reported to have the highest affinity for the CB1 receptor (fentomolar) during *in vitro* tests, it showed no inhibition when administered orally.<sup>197,198</sup> This outcome is probably due to poor biodistribution of the compound *in vivo*. Recently, extensive studies have been reported towards the development of novel CB1 ligands by changing the central core of rimonabant to an imidazole, triazole, or phenyl unit (**O-183**). Other development programmes have produced non-rimonabant-based scaffolds as promising therapeutic scaffolds *e.g.* **CP-945598** (Pfizer), **MK-0364** (Merck) and **AVE-1625** (Sanofi-Aventis) (Scheme 3.1.1).



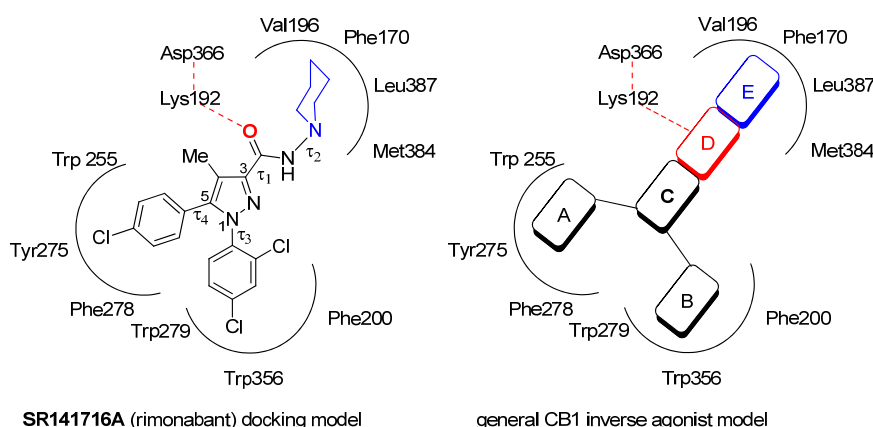
**Scheme 3.1.1.** Drug-like potential CB1 antagonists

Clinical trials of rimonabant for treatment of obesity were promising and the compound was approved by the European Medicines Agency for sale in Europe as Acomplia in 2006. Although few side-effects were reported during the trial, several serious psychiatric disorder cases emerged once the drug was available clinically.

Consequently, this drug was withdrawn from the market in 2008 and many ongoing projects targeting the CB1 receptor as a strategy for developing anti-obesity drugs were also terminated.<sup>199</sup>

### 3.1.3 Conformational analysis of rimonabant and computational modelling of its binding features with the CB1 receptor

Amongst several potent anti-obesity drugs either on the market or in development, **SR141716A** has received the most attention and been subjected to the most comprehensive pharmacological studies. As a result, it is now categorised as an inverse agonist\* of the CB1 receptor exhibiting negative intrinsic activity to the endocannabinoid system.<sup>200-202</sup> Conformational analysis of rimonabant reveals that it has several distinct conformational minima (Scheme 3.1.2).<sup>203</sup>



**Scheme 3.1.2.** Rimonabant docked in the helical binding site of the CB1 receptor and a general inverse agonist-receptor interaction model.<sup>203</sup>

In particular, conformations in which torsional angle  $\tau_1$  about the bond between the pyrazole ring and the acyl hydrazine carbonyl is *s-trans*, and the torsional angle  $\tau_2$  about the N-N bond of the hydrazine unit, is in one of four specific values are favoured. The torsional angles  $\tau_3$  and  $\tau_4$  describe the conformation of the two aryl groups, and these vary depending on the substituents on these rings.<sup>204</sup>

\* *Agonist*: a term used to describe a type of ligand or drug that binds to a receptor and stimulates its activity. *Inverse agonist*: a term used to describe a type of ligand or drug that binds to a receptor and elicits the opposite response to an agonist (*i.e.* reduces its intrinsic/constitutive activity to sub-basal levels). *Antagonist*: A term used to describe a type of ligand or drug that binds to a receptor and blocks all ligand-induced activity (*i.e.* it will restore basal intrinsic/constitutive activity).

Computational modelling by docking of rimonabant in a minimised energy conformation with the TMH domains of CB1 suggested an essential salt bridge between the carbonyl moiety and Lys192Asp366.<sup>205</sup> Further computational binding analysis based on structure-activity relationships (SAR) of similar pharmacophores to rimonabant allowed a general model for CB1 inverse agonist binding to be constructed.

Besides the crucial salt bridge formed between the carbonyl group of rimonabant and Lys192Asp366, the binding interactions were reinforced by  $\pi$ - $\pi$  stacking interactions between the two substituted phenyl groups and the aromatic-rich TMH 3-6 regions of the CB1 receptor. In addition, a lipophilic interaction was contributed by the piperidinyl group and by the hydrophobic cavity comprised of Val196, Phe170, Leu387 and Met384.

It is not clear what mechanism caused the psychiatric effects. However, as the endocannabinoid system is known to be involved in our ability to manage stress and anxiety, prohibition of this pathway may result in depression. Elaboration of the psychiatric functions controlled by the endocannabinoid system will be necessary if the effects caused by blocking the receptor are to be fully understood.

#### **3.1.4 Conventional methods for preparation of radio-labelled pharmaceuticals for imaging the CB1 receptor**

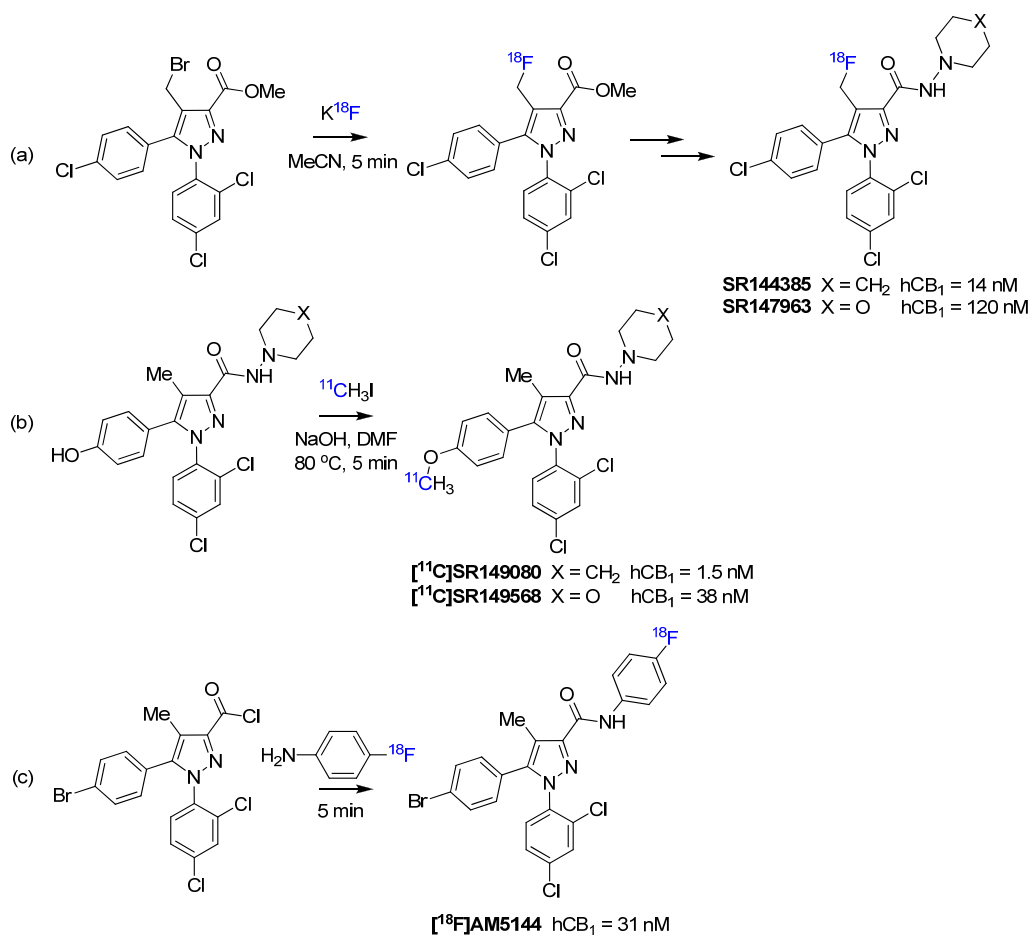
Non-invasive examination of the brain by molecular imaging technologies such as PET and SPECT require high-affinity radio-labelled ligands as tracers. The scaffold of rimonabant constitutes a promising starting point for the development of such tracers.

##### **3.1.4.1 Radio-labelling of the rimonabant scaffold by nucleophilic substitution**

According to the general binding model of rimonabant with the CB1 receptor, labelling tactics have been focused on introducing labels at the 4-methyl, 5-aryl and 3-carboxamide moieties in order to retain the bioactivity of the modified tracers. In addition, minor modifications to the substrate provide opportunities to enhance

lipophilicity and affinity to achieve better biodistribution.

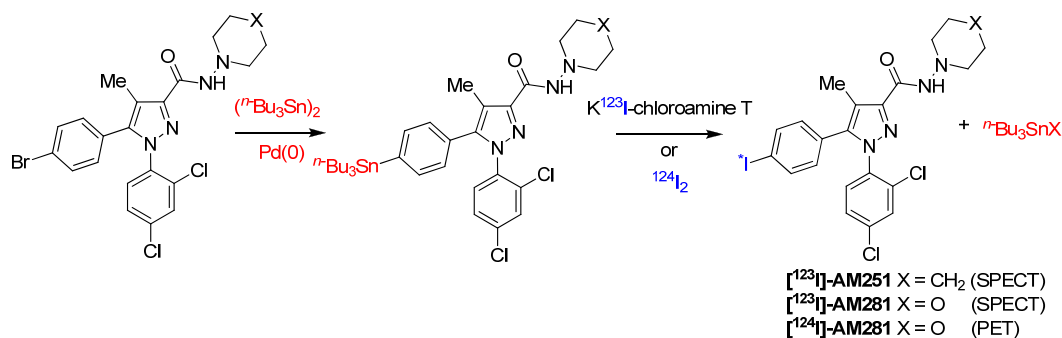
Mathews reported the preparation  $^{18}\text{F}$  and  $^{11}\text{C}$ -labelled analogues by means of nucleophilic substitution reactions.<sup>206,207</sup> Galety described replacing the 3-acyl hydrazine unit with a  $[\text{}^{18}\text{F}]$ -4-fluorophenyl amide unit; the  $[\text{}^{18}\text{F}]$ -4-fluorophenylaniline was obtained by a  $\text{S}_{\text{N}}\text{Ar}$  reaction of dinitrobenzene with  $^{18}\text{F}$  anions.<sup>208</sup> Pharmacological data for these tracer candidates revealed good inhibition of the CB1 receptor in their unlabelled form. Moreover, the  $^{18}\text{F}$  and  $^{11}\text{C}$ -labelled ligands provided high quality scanning images. However, the short half-life of these radio-nuclei limited the range of possible applications for these tracers (Scheme 3.1.3).



**Scheme 3.1.3** Mathews' (a and b) and Galety's approaches (c) for preparation of radio-labelled rimonabant analogues for PET scanning.<sup>206-208</sup>

### 3.1.4.2 Radio-labelling of rimonabant by *ipso*-iododestannylation

As indicated previously, [ $^{123}\text{I}$ ]-AM251 exhibits similar binding affinity to rimonabant and has been used in animal models for SPECT scanning. Another candidate, [ $^{123}\text{I}$ ]-AM281 was also prepared for this purpose and was the first SPECT agent for visualising the human cannabinoid system.<sup>209</sup> The general method used to synthesise aryl iodinated CB1 ligands is to employ *ipso*-iododestannylation of the corresponding aryltributylstannane precursors with various iodonium electrophiles such as a mixture of KI and chloroamine-T or molecular iodine. The arylstannanes are generally prepared by coupling of the corresponding aryl bromides with hexabutyldistannane using a catalytic amount of Pd(0). [ $\text{I}^{124}$ ]-AM281 for PET imaging was prepared in this fashion (Scheme 3.1.4).<sup>210</sup>



**Scheme 3.1.4.** Preparation of radio-iodinated imaging agents *via ipso*-iododestannylation.<sup>210</sup>

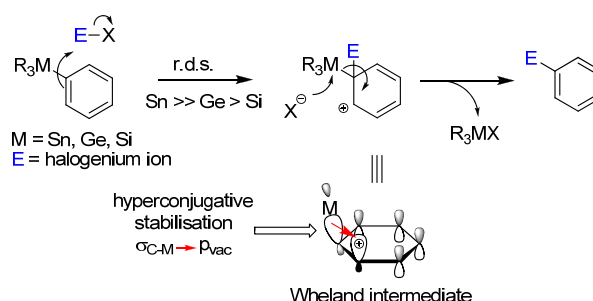
Tedious post-reaction purification procedures are critical and necessary to remove Sn and Pd containing residues prior to administration of the labelled analogues for *in vivo* trials. The time required for this purification degrades the quality of the tomographic images due to attenuation of the activity of the radio-iodinated compounds. Additionally, preparation of these analogues for screening as potential imaging agents relies on individual synthetic processes in solution.<sup>211</sup>

### 3.1.5 Mechanism of *ipso*-halodemetalation

The stabilisation of  $\beta$ -carbocations by group 14 organometallics is known as the  $\beta$ -effect.<sup>212</sup> The stabilisation accrues from orbital overlap of the  $\sigma_{\text{C-M}}$  orbital with the empty p orbital of the carbocation ( $p_{\text{vac}}$ ). This phenomenon is known as hyperconjugative stabilisation. Eaborn conducted kinetic studies to rank the

reactivity of aryl-group 14 metal bonds with electrophiles. The relative rate of cleavage the aryl-metal bonds with acid was as follows:  $R_3Sn-Ar$  is cleaved  $10^4$  times faster than  $R_3Ge-Ar$  which is cleaved  $10^2$  times faster than  $R_3Si-Ar$ .<sup>213</sup>

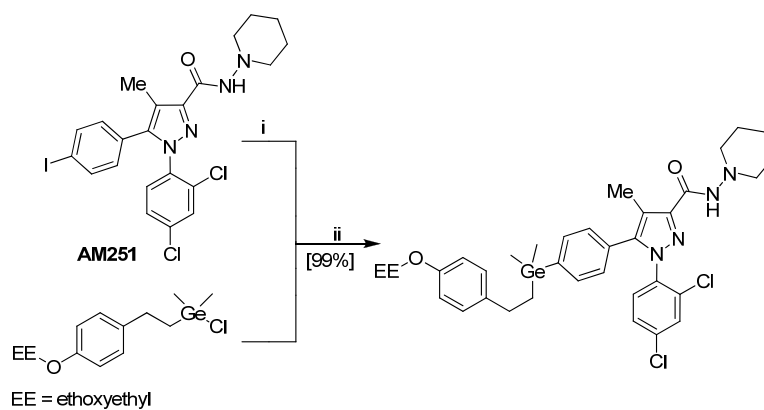
Upon treatment of aryl group 14 organometallics with electrophiles, an  $sp^2$  hybridised carbocation is generated  $\beta$  to the C-M bond in the Wheland intermediate and this is stabilised by  $\sigma_{C-M} \rightarrow p_{vac}$  hyperconjugation. Subsequently, the C-M bond is cleaved by nucleophilic attack at the metal centre by the electrophile counter-ion to afford an *ipso*-substituted aromatic and the metallic residue. This process is known as *ipso*-halodemetalation when halonium ions are involved. The reaction is highly regioselective as the result of the strong  $\beta$ -effect (Scheme 3.1.5).



**Scheme 3.1.5.** Mechanism of *ipso*-halodemetalation.

### 3.2 Preliminary Results – Prior work in the group

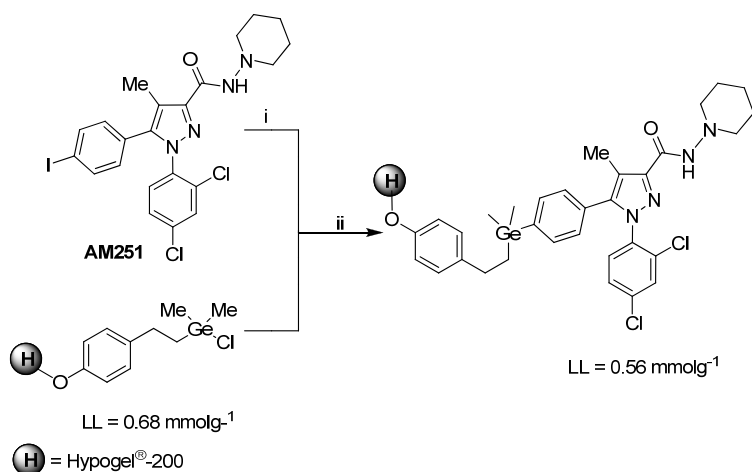
The development of a new protocol to facilitate iodination of diarylpyrazole CB1 ligands by *ipso*-iododegermylation of a germyl-linker bound precursor was initiated by Teyrnon Jones (Spivey group, 2000-2004)<sup>214</sup> with the original plan being to look at both solution and solid-phase approaches. Jones had been able to prepare the diarylpyrazole germane linker in 99 % yield by using  $iPrMgCl$  mediated iodine-magnesium exchange on **AM251** then transmetallation with a model linker arylgermyl chloride. This pyrazole germane was chosen as a precursor for the investigation of *ipso*-iododegermylation reactions (Scheme 3.2.1).



**Scheme 3.2.1.** Jones' preparation of an arylpyrazole germane adduct to investigate *ipso*-iododegermylation reactions.<sup>214</sup>

*Reagents and conditions:* i)  $t\text{PrMgCl}$ ,  $-40\text{ }^{\circ}\text{C}$ -RT, 2 h; ii) THF, RT, 16 h.

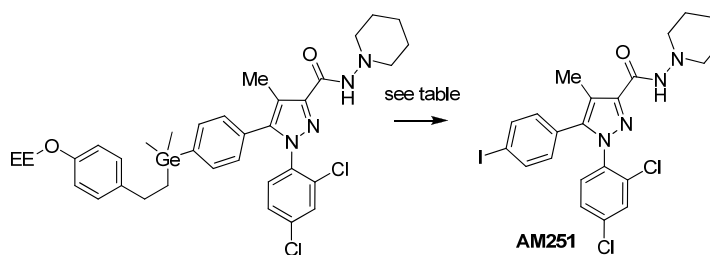
An analogue of solid-supported diarylpyrazole germyl linker was also prepared by the same method using Hypogel<sup>®</sup>-200 as the polymer support (Scheme 3.2.2).



**Scheme 3.2.2.** Jones' immobilisation of diarylpyrazole acyl hydrazide on germyl Hypogel<sup>®</sup>-200 functionalised resin.<sup>214</sup>

*Reagents and conditions:* i)  $t\text{PrMgCl}$ ,  $-25\text{ }^{\circ}\text{C}$ -RT, 2 h; ii) THF, RT, 16 h.

*ipso*-Iododegermylation was attempted on the solution model system using NaI in combination with various oxidants as well as with ICl (Table 3.2.1).

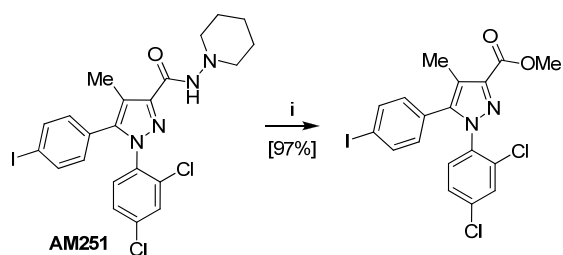


| Entry | Conditions                                         | Outcome                                                      |
|-------|----------------------------------------------------|--------------------------------------------------------------|
| 1     | NaI, Dichloramine T, AcOH, 1 h, RT                 | No <b>AM251</b><br>No Ge-linker recovered                    |
| 2     | NaI, Chloramine T, AcOH, 1 h RT                    | <b>AM251</b> and oxidised<br>by-product formed               |
| 3     | NaI, H <sub>2</sub> O <sub>2</sub> , MeOH, 1 h, RT | <b>AM251</b> and oxidised<br>by-product formed               |
| 4     | NaI, Selectfluor <sup>TM</sup> , MeOH, RT, 0,5 h   | No reaction                                                  |
| 5     | ICl, CH <sub>2</sub> Cl <sub>2</sub> , 1 h, RT     | 36 % yield of <b>AM251</b> and<br>oxidised by-product formed |

**Table 3.2.1** Jones' attempted electrophilic iodination mediated pyrazole-germane cleavage to furnish **AM251**.<sup>214</sup>

No **AM251** was found using the combination of NaI-dichloroamine T (DCT) in HOAc at RT although the pyrazole germane substrate was consumed (entry 1). NaI-chloroamine T and NaI-H<sub>2</sub>O<sub>2</sub> combinations gave the desired **AM251** but contaminated with unidentified by-products due to over oxidation (entries 2 and 3). No reaction occurred when NaI was used with Selectfluor<sup>TM</sup> as an oxidant (entry 4). Treatment of the pyrazole germane at high dilution with ICl solution in CH<sub>2</sub>Cl<sub>2</sub> gave a 36 % yield of **AM251** contaminated with several by-products (entry 5). The diarylpyrazole germane resin was also subjected to the ICl conditions but none of the desired product was found in the filtrate.

To identify the over oxidation process, compound **AM251** was subjected to DCT in MeOH for 1 h. This reaction gave the corresponding methyl ester in 97 % yield (Scheme 3.2.3).



**Scheme 3.2.3.** Jones' DCT facilitated oxidative cleavage of the acyl hydrazide with **AM251**.<sup>211</sup>

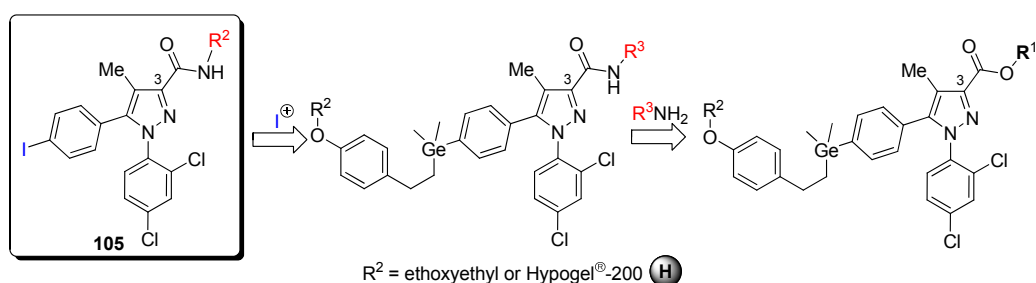
*Reagents and conditions:* i) DCT, MeOH, RT, 1 h.

This experiment demonstrated that achieving *ipso*-iododegermylation on this substrate using NaI as the source of label was going to require an oxidant which could oxidise iodide to iodonium but not effect oxidative cleavage of the acyl hydrazide.

### 3.3 Aims and objectives

We became interested in developing a novel strategy for efficient, transition metal free, parallel synthesis of iodinated CB1 ligands based upon *ipso*-iododegermylation of solid supported arylgermane precursors. ‘Proof-of-concept’ for this notion is described in the following sections.

Cognisant of the findings described above, it was envisaged to develop a new protocol for immobilisation of diarylpyrazole units onto solid-supported germyl functionalised resins that could allow diversification in a parallel fashion on the resin. Iodinated rimonabant analogues **105** were expected to be furnished in a pure form following electrophilic iodination under appropriate conditions (Scheme 3.3.1).



**Scheme 3.3.1.** Proposed approach to iodinated rimonabant analogues **105**.

Towards these ends, the following, specific objectives for the project were identified:

- 1) To build a diarylpyrazole germane model molecule in solution with an ester at C-3 to allow for further functionalisation.
- 2) To screen suitable conditions to facilitate *ipso*-iododegermylation leading to the desired products.
- 3) To immobilise the diarylpyrazole unit onto a solid-support and conduct parallel synthesis of iodinated rimonabant analogues.

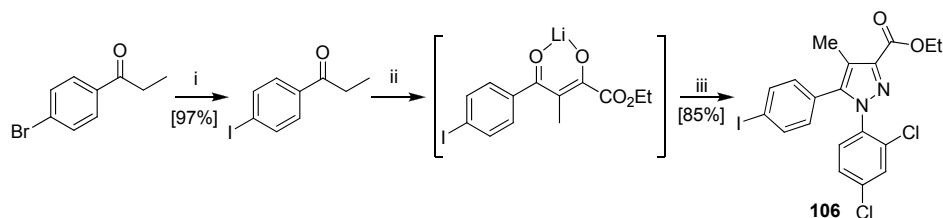
Progress towards these objectives is described in the following section.

### 3.4 Result and discussion

#### 3.4.1 Synthesis of AM281 in solution phase *via ipso-iododegermylation*

It was planned to prepare a rimonabant analogue containing an aryl iodide for attachment to the solid support *via* a germyl-linker and having an ester at C-3 to allow for variation of the functionality at this position after immobilisation but before *ipso*-iododegermylation. It was envisaged that the immobilisation step could be achieved using Knochel's iodine-magnesium exchange procedure which requires an aryl iodide as substrate. Thus, preparation of 4-iodopropiophenone as starting material was demanded.

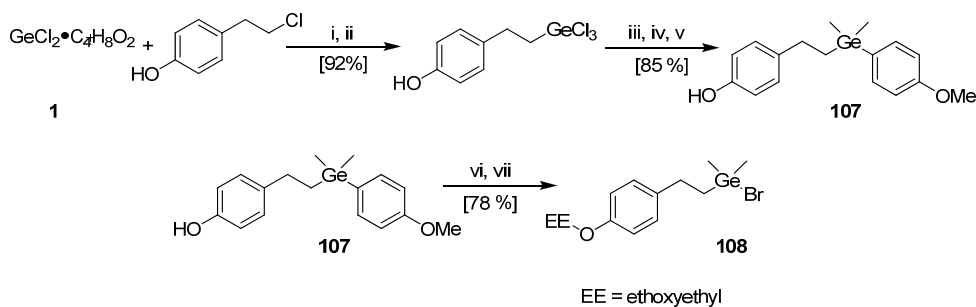
Commercially available 4-bromopropiophenone was converted into 4-iodopropiophenone by Buchwald's catalytic aromatic Finkelstein reaction in the presence of NaI and CuI as a catalyst.<sup>215</sup> 4-Iodoacetophenone was enolised with LHMDS at 0 °C and then quenched with diethyl oxalate to afford  $\beta$ -ketoester lithium salt. The lithium salt was treated with 2, 4-dichlorohydrazine hydrochloride in 95 % EtOH with 0.5 mL of conc. HCl and stirred for 16 h at RT followed by re-suspension in glacial acetic acid and refluxing for another 16 h to furnish iodoarylpyrazole ethyl ester **106** in 82 % over three steps (Scheme 3.4.1).<sup>211</sup>



**Scheme 3.4.1.** The preparation of 1,5-diaryl pyrazolyl ethyl ester **106**.

*Reagents and conditions:* i) NaI, CuI, *N,N'*-dimethylethylenediamine, 1,4-dioxane, 100 °C, 16 h; ii) LHMDS, 0 °C, 1 h then ethyl oxalate, rt, 16 h; iii) 2, 4-dichlorohydrazine hydrochloride, 95 % EtOH, conc. HCl (0.5 mL), rt, 16 h then HOAc, reflux, 16 h.

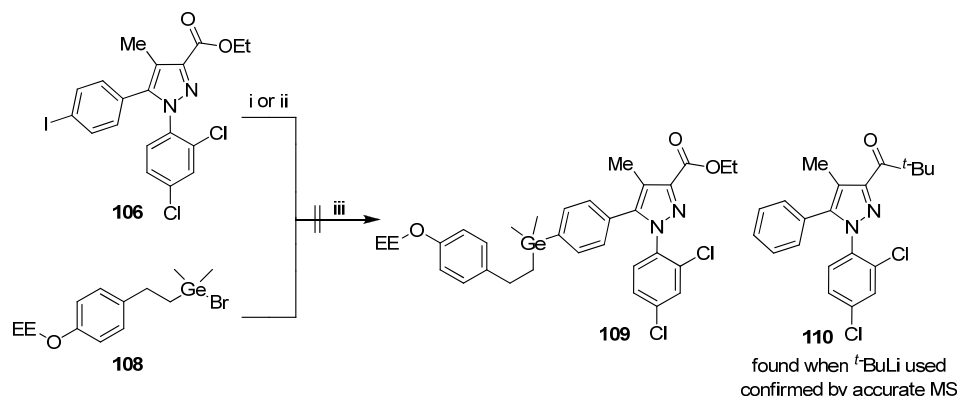
Germyl linker precursor **107** was prepared according to the literature procedure published by our group.<sup>138</sup> Alkylation of the phenolic hydroxyl group with an ethoxyethyl (EE) group followed by subjection to conc. HBr afforded germyl bromide linker **108** in 61 % overall yield over 6 steps from GeCl<sub>4</sub>. The EE group on this germyl linker is designed to mimic the PEG graft on HypoGel<sup>®</sup>-200 resin (Scheme 3.4.2).



**Scheme 3.4.2.** The preparation of germyl bromide linker **108**.

*Reagents and conditions:* i) sealed tube, 150 °C, 16 h; ii) conc. HCl, rt, 16 h; iii) 4-methoxyphenylmagnesium bromide 0.5 M in THF, reflux, 4 h; iv) conc. HCl, rt, 16 h; v) methyllithium, -40 °C – rt, 16 h; vi) 1-chloro-2-ethoxyl ethane, K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C, 24 h; vii) conc. HBr, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h.

Attempts to prepare diarylpyrazole germane **109** by means of iodine-metal exchange of iodoarylpyrazole ethyl ester **106** at low temperature then cannulation of the resulting aryl metal species into a solution of germyl bromide linker **108** were unsuccessful. Various of organometallics such as <sup>i</sup>PrMgCl, <sup>i</sup>PrMgCl-LiCl complex<sup>216</sup> and <sup>t</sup>BuLi were employed but neither expected product nor starting materials were recovered, despite the fact that <sup>i</sup>PrMgCl had been employed previously to perform a closely similar transformation in the case of iodoarylpyrazole acyl hydrazide by Jones as described above (Scheme 3.4.3).



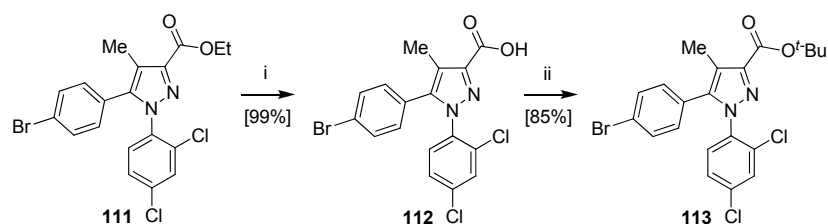
**Scheme 3.4.3.** Attempts to prepare diarylpyrazole germane **109** *via* iodine-metal exchange of iodoarylpyrazole ethyl ester **106** mediated by various organometallics.

*Reagents and conditions:* i) <sup>i</sup>PrMgCl or <sup>i</sup>PrMgCl-LiCl complex, THF, -40 °C-RT 2 h; ii) <sup>t</sup>BuLi, -78 °C, 2h; iii) THF, RT, 16 h.

Inspection of the MS spectrum from the crude reaction mixture from the reaction using <sup>t</sup>BuLi as metalating reagent revealed the possibility that formation of the diarylpyrazole *tert*-butyl ketone **110** was occurring. This suggested that the ethyl

ester at C-3 in the pyrazole substrate **106** was susceptible to nucleophilic addition even at the low temperatures employed. It was decided to employ a sterically hindered *tert*-butyl ester to suppress this undesired side-reaction. Moreover, as Oshima has used  ${}^i\text{Pr}^n\text{Bu}_2\text{MgLi}$  to mediate metalation of polyfunctionalised aryl bromides,<sup>217</sup> we decided to employ this reagent on the bromo diarylpyrazole which could be obtained directly from commercially available starting material. Consequently, bromodiarylpyrazole ethyl ester **111** was prepared in 88 % overall yield according to the same procedures shown for the iodide analogue in Scheme 3.4.1.

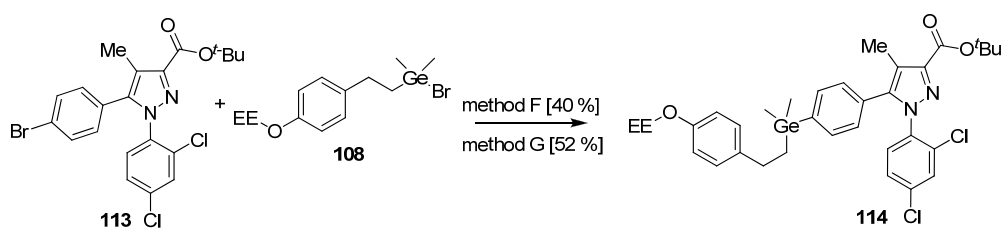
Bromoarylpyrazole ethyl ester **111** was then saponified to give bromoarylpyrazole carboxylic acid **112** which was converted to *tert*-butyl ester **113** in 84 % yield by using *tert*-butyl 2,2,2-trichloroacetimidate (TBTA) and a catalytic amount of  $\text{BF}_3\cdot\text{Et}_2\text{O}$  in cyclohexane at RT for 16 h (Scheme 3.4.4).<sup>218</sup>



**Scheme 3.4.4.** The preparation of bromoarylpyrazole *tert*-butyl ester **113**.

*Reagents and conditions:* i)  $\text{NaOH}$ ,  $\text{THF-H}_2\text{O}$  (4:1 v/v), 70 °C, 6 h; ii) *tert*-butyl 2,2,2-trichloroacetimidate, cat.  $\text{BF}_3\cdot\text{Et}_2\text{O}$ , cyclohexane, RT, 16 h.

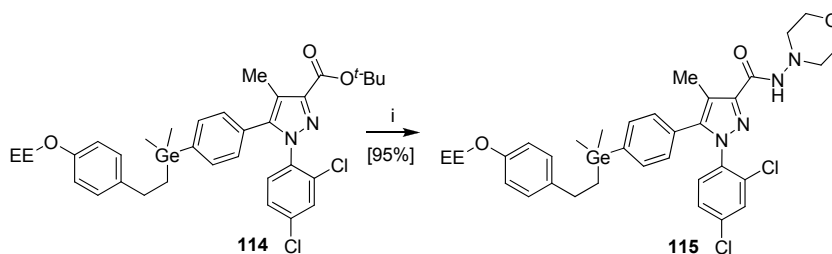
The pyrazole *tert*-butyl ester **113** was subjected to metalation with Oshima's bimetallic reagent followed by cannulation to a solution of arylgermane bromide **108** in THF at -78 °C before warming to RT. This gave the desired diarylpyrazole germane **114** in 12 % yield. By pre-mixing the pyrazole *tert*-butyl ester **113** and the germynyl bromide **108** to achieve *in situ* metalation/functionalisation of germane bromide **108**,<sup>156</sup> a 40 % yield of the target pyrazole germane **114** was obtained using the  ${}^i\text{Pr}^n\text{Bu}_2\text{MgLi}$  complex. Moreover, pyrazole germane could also be prepared in up to 52 % yield using these Barbier conditions with  ${}^t\text{BuLi}$  as the metalating reagent (Scheme 3.4.5).



**Scheme 3.4.5.** Preparation of diarylpyrazole germane **114**.

*Reagents and conditions:* method F:  $t\text{-Pr}^n\text{Bu}_2\text{MgLi}$ , THF,  $-78\text{ }^\circ\text{C}$ -RT, 16 h; method G:  $t\text{-BuLi}$ , THF,  $-78\text{ }^\circ\text{C}$ -RT, 16 h.

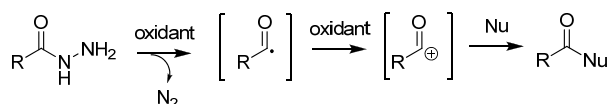
Direct amidation of the *tert*-butyl ester in pyrazole germane **114** with *N*-aminomorpholine under basic conditions gave the corresponding acyl hydrazide **115** in 95 % yield (Scheme 3.4.6).



**Scheme 3.4.6.** Amidation of pyrazole germane **115**.

*Reagents and conditions:* i) *N*-aminomorpholine, LHMDs, THF, RT, 2 h.

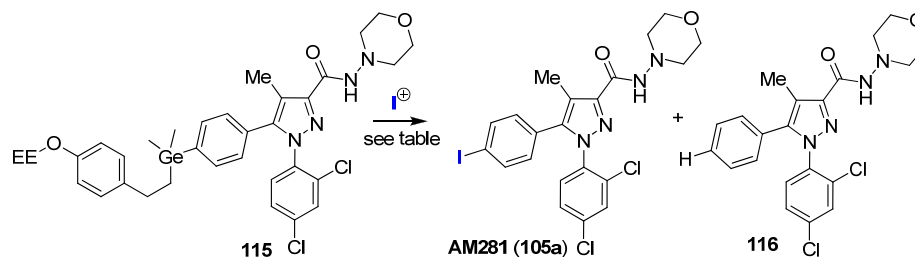
Acyl hydrazide **115** was used as a model substrate on which to screen suitable conditions to achieve *ipso*-iododegermylation. The previous unsuccessful attempts using this substrate reported by Jones were plagued by over oxidation of the acyl hydrazide moiety leading to formation of methyl ester containing products and relative carboxylic acid derivatives.<sup>214</sup> Oxidative acyl hydrazide cleavage has been studied by Smith, who has proposed that the process is initiated by formation of an acyl radical intermediate with extrusion of nitrogen gas. The acyl radical then suffers further oxidation to give an acyl cation which is rapidly trapped with nucleophiles giving carboxylic acid derivatives (Scheme 3.4.7).<sup>219</sup>



**Scheme 3.4.7.** Smith's proposed mechanism for oxidative acyl hydrazide cleavage.<sup>219</sup>

New oxidation conditions needed to be identified that would mediate cleavage of the aryl-Ge bond but avoid degradation of the acyl hydrazide moiety.

*ipso*-Iododegermylation conditions based on many electrophilic iodination conditions were evaluated (Table 3.4.1).



| Entry | Conditions <sup>a</sup>                              | Yield (%)       |
|-------|------------------------------------------------------|-----------------|
| 1     | NaI, chloramine T, AcOH, 16 h, rt                    | 0 <sup>c</sup>  |
| 2     | I <sub>2</sub> , CCl <sub>4</sub> , 16 h, rt         | 0 <sup>c</sup>  |
| 3     | NaI, FeCl <sub>3</sub> , 16 h, rt                    | 0 <sup>c</sup>  |
| 4     | ICl, 16 h, rt                                        | 0 <sup>c</sup>  |
| 5     | NH <sub>4</sub> I, Oxone <sup>®</sup> , 16 h, rt     | 0 <sup>c</sup>  |
| 6     | NaI, 3-CPBA, 16 h, rt <sup>b</sup>                   | 0 <sup>d</sup>  |
| 7     | NaI, AcO <sub>2</sub> H, AcOH, 16 h, rt <sup>b</sup> | 0 <sup>d</sup>  |
| 8     | I <sub>2</sub> , 3-CPBA, HOAc <sup>b</sup>           | 0 <sup>d</sup>  |
| 9     | NIS, TFA (cat.), HOAc, 16 h, rt                      | 0 <sup>d</sup>  |
| 10    | I <sub>2</sub> , HOAc, rt, 16 h                      | 15 <sup>e</sup> |
| 11    | I <sub>2</sub> , TFA-HOAc, 16 h, rt <sup>f</sup>     | 63 <sup>e</sup> |
| 12    | NaI, NCS, TFA-AcOH, 30 min, rt <sup>f</sup>          | 85              |

<sup>a</sup> All reactions were carried out with 2 eq of reagents. <sup>b</sup> slow addition of peracids <sup>c</sup> No reaction occurred, recovery of S.M. <sup>d</sup> decomposition of S.M. <sup>e</sup> concomitant with by-product **116** (see text).<sup>f</sup> TFA-HOAc (1:3 v/v).

**Table 3.4.1** Screening for *ipso*-iododegermylation of acyl hydrazide **115** in solution phase.

Initial studies employed iododestannylation conditions reported by Gatley using I<sub>2</sub>/CCl<sub>4</sub><sup>220</sup> and chloramine-T/NaI<sup>221</sup> at RT for 16 h (entries 1 and 2). However, none of these conditions gave the desired iodinated aryl pyrazole **AM281 (105a)**; starting material was recovered. Identical results were obtained using NaI/FeCl<sub>3</sub>,<sup>222</sup> NH<sub>4</sub>I/Oxone<sup>®223</sup> and ICl as iodination agents (entries 3-5), although interestingly ICl has been reported to prepare aryl iodides from arylsilanes,<sup>224</sup> which are generally less reactive than arylstannanes and arylgermanes.<sup>213</sup> Nevertheless, arylgermane linker **115** was recovered quantitatively from all these reactions.

Next, attention focused on investigating peracids as alternative oxidants for *ipso*-iododegermylation. Accordingly, arylgermane-linker **115** was treated with NaI/3-CPBA,<sup>225</sup> NaI/AcO<sub>2</sub>H and I<sub>2</sub>/3-CPBA. In all cases, slow addition of the peracids to the reaction mixtures was employed. Unfortunately, neither iodinated aryl pyrazole **AM281 (105a)** nor unreacted arylgermane **115** could be isolated following these reactions (entries 6-8). A similar outcome was also observed when *N*-iodosuccimide (NIS) was used with catalytic amount of TFA (entry 9).

Moerlein has described *ipso*-iododegermylation of arylgermanes using I<sub>2</sub> promoted by HOAc. The success at this protocol is probably due to the polarization of I<sub>2</sub> by the acid and stabilization of the transition state of the reaction by HOAc.<sup>226</sup>

Upon subjecting arylgermane-linker **115** to I<sub>2</sub>-HOAc, a slow reaction (16 h) was observed which yielded the iodinated aryl pyrazole **AM281 (105a)** in 15 % yield along with *ipso*-protodegermylation by-product **116** in 10 % yield (entry 10). The by-product is presumably formed due to protonolysis under these acidic conditions. This positive result encouraged us to optimize the conditions. TFA was used as co-solvent to enhance the polarization of I<sub>2</sub>, and iodinated aryl pyrazole **AM281 (105a)** was obtained in 63 % yield. Again, the protonated contaminated **116** was isolated in 10 % yield (entry 11).

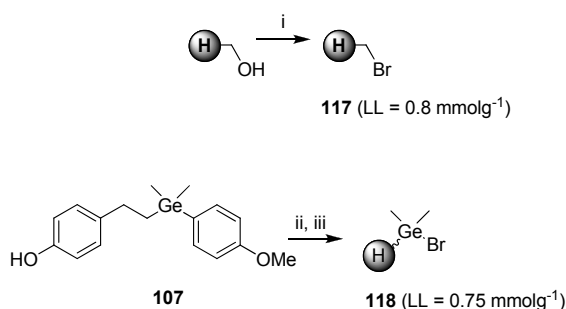
Further optimization of the reaction was achieved by using NaI and *N*-chlorosuccimide (NCS) in the TFA-HOAc reaction medium for 30 min, affording iodinated aryl pyrazole **AM281 (105a)** in 85 % yield. No by-product **116** could be detected under these conditions (entry 12).<sup>227</sup> This significantly optimised protocol is ideal for the final approach toward parallel synthesis of iodinated rimonabant analogues **105** using a germyl-functionalised solid support as it is rapid and uses NaI as the source of iodine. Radioactive NaI is much more readily available than other iodination reagents.

### 3.4.2 Solid-phase, parallel synthesis of iodinated rimonabant analogues

Building upon the successful development of conditions for *ipso*-iododegermylation in solution, it was necessary to apply the same chemistry on the solid-phase. Hypogel<sup>®</sup>-200 resin was chosen for this task. Hypogel<sup>®</sup> is a PEG grafted polystyrene

resin with better swelling properties in hydrophilic solution than Merrifield resin. The swelling property of the chosen resin was envisioned to be an essential parameter to reproduce our iodination reaction which proceeds in a highly polar solvent system.

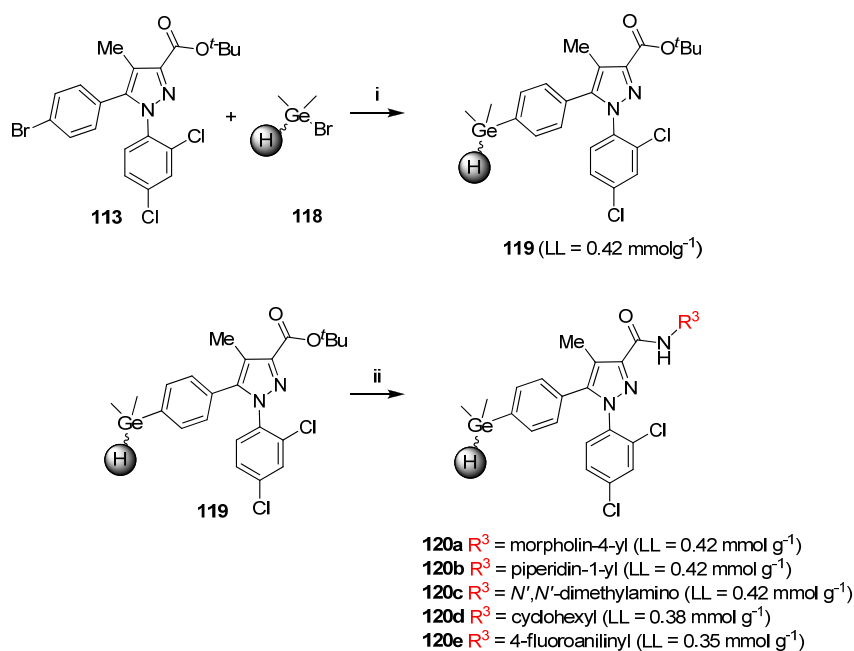
Conversion of Hypogel<sup>®</sup>-OH (0.8 mmol g<sup>-1</sup>) to Hypogel<sup>®</sup>-Br **117** (0.8 mmol g<sup>-1</sup>) proceeded quantitatively using a combination of PPh<sub>3</sub> and CBr<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub>. Attachment of germyl linker **107** was achieved using Williamson etherification,<sup>138</sup> and the resulting resin was converted into the germyl bromide resin **118** utilising 48 % HBr in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 3.4.8).



**Scheme 3.4.8.** Preparation of germyl functionalised resin **118**.

*Reagents and conditions:* i) PPh<sub>3</sub>, CBr<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C-RT, 24 h; ii) **117**, K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C, 24 h; iii), conc. HBr, CH<sub>2</sub>Cl<sub>2</sub>, RT, 16 h.

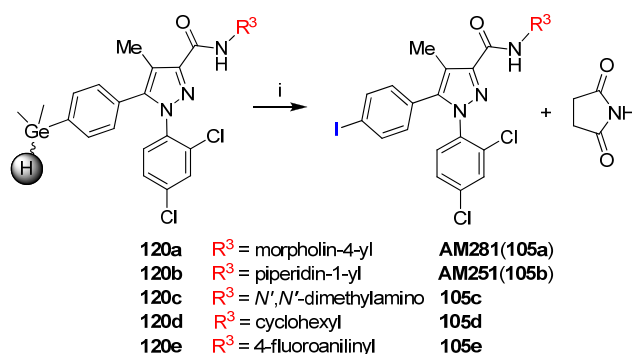
Immobilisation of diarylpyrazole **113** onto the germyl functionalised resin **118** was achieved according to the method developed in solution (see Scheme 3.4.5) *via* bromine-lithium exchange on the pyrazole substrate **113** in the presence of the germyl bromide resin **118**. Amidation of the forming resin **119** with selected hydrazines and amines facilitated by LHMDs, allowed synthesis of a library of five functionalised diarylpyrazolyl resins **120a-e** (Scheme 3.4.9).



**Scheme 3.4.9.** Parallel preparation of C-3 functionalised pyrazole resins **120a-e**.

*Reagents and conditions:* i) <sup>t</sup>BuLi, THF, -78 °C-RT, 16 h; ii) R<sup>3</sup>NH<sub>2</sub>, LHMDS, THF, RT, 16 h.

The Ge resins were swollen in separate vessels with CH<sub>2</sub>Cl<sub>2</sub> in reaction cartridges in the presence of NaI, before addition of a solution of NCS in TFA-HOAc at RT. After filtering off the resin beads, iodinated rimonabant analogues **105a-e** were isolated from reaction mixture in good yields (Table 3.4.2).



| Entry | Substrate | Time (h) | Product             | Yield <sup>a</sup> (%)  | Overall yield <sup>b</sup> (%) |
|-------|-----------|----------|---------------------|-------------------------|--------------------------------|
| 1     | <b>a</b>  | 1        | <b>AM281 (105a)</b> | 63                      | 38                             |
| 2     | <b>b</b>  | 1        | <b>AM251 (105b)</b> | 60                      | 33                             |
| 3     | <b>c</b>  | 1        | <b>105c</b>         | 60                      | 33                             |
| 4     | <b>d</b>  | 1        | <b>105d</b>         | 55                      | 28                             |
| 5     | <b>e</b>  | 6        | <b>105e</b>         | 42                      | 19                             |
| 6     | <b>b</b>  | 5 min    | <b>AM251 (105b)</b> | 8 (1 <sup>st</sup> run) | 4.4                            |
| 7     | <b>b</b>  | 5 min    | <b>AM251 (105b)</b> | 5 (2 <sup>nd</sup> run) | 2.8                            |

<sup>a</sup>isolation yields of the *ipso*-iododegermylation step

<sup>b</sup>deductive from immobilisation of diarylpyrazole **113** onto the germyn resin **118** to aryl pyrazole **105**

**Table3.4.2.** Parallel preparation of iodinated C-3 functionalised pyrazoles.

*Reagents and conditions:* i) NaI, NCS, TFA-HOAc (1:3 v/v), RT.

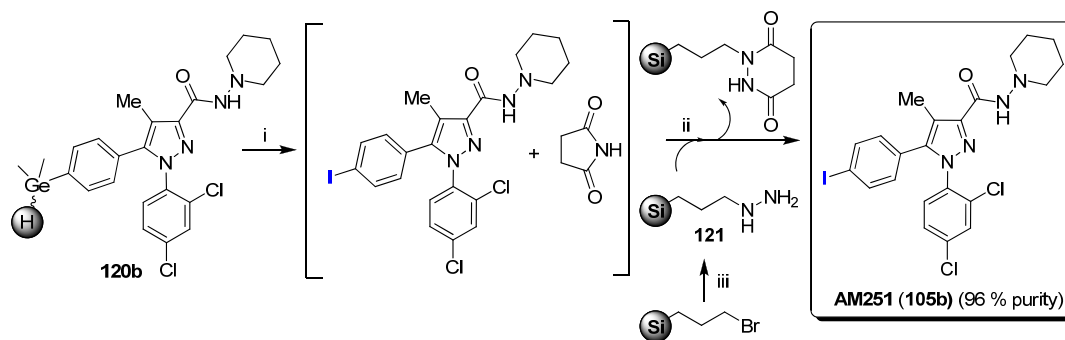
The *ipso*-iododegermylation of aryl pyrazolyl germane resins **120a-d** were completed within 1 h (entries 1-4) whereas, the 4-fluoroanilinyll functionalised pyrazolyl resin **120e** required significantly longer (6 h, entry 5).

A short exposure of resin **120b** to the iodination conditions furnished iodinated aryl pyrazole **AM251 (105b)** in 8 % after column chromatography (entry 6). In addition, re-subjecting the resin **120b** used for entry 6 to the iodination conditions for 5 min gave an additional 5 % of the desired product. These results confirmed that the protocol should be suitable for ‘hot chemistry’ and provide sufficient quantities of radio iodinated tracer within a short period of time for imaging.

Analysis of the crude iodinated aryl pyrazole **AM251 (105b)** directly after filtration by means of HPLC (UV detector set at 254 nm) revealed a 75 % purity of the desired product contaminated with the succinimide by-product from the NCS. As it is crucial to remove by-products prior to injection for *in vivo* tests, an efficient and rapid separation process needed to be developed.

It was decided to develop a nucleophilic scavenger resin to effect *in situ* removal of the succinimide. Hydrazine-functionalised Hypogel<sup>®</sup>-200 was initially selected for this purpose. Thus, treatment of Hypogel<sup>®</sup>-Br **117** with hydrazine hydrate and K<sub>2</sub>CO<sub>3</sub> in DMF for 16 h gave a resin of this type. To test the scavenging ability of this hydrazine resin, a freshly prepared crude mixture of iodinated aryl pyrazole **AM251** (**105b**) was treated with the resin in refluxing EtOH for 1 h. The resin was then filtered off, and the organic fraction was subjected to HPLC to quantify its purity. The chromatograph showed fairly efficient removal of succinimide (only 5 % remaining in the mixture) but the trace also showed new impurities in the sample. Polystyrene and Merrifield-based hydrazine resin gave the same outcome. The new impurities were non-polar and highly UV active moieties apparently arising from degradation of the polymer-supports. A literature search revealed that the liberation of these residues from resins under similar reaction or cleavage conditions has been noted previously.<sup>228,229</sup>

Gratifyingly, treatment of the crude reaction mixture containing iodinated aryl pyrazole **AM251** (**105b**) with a *Si*-propyl hydrazine solid-support **121** gave a clean HPLC trace free from the aforementioned impurities, and quantified as containing iodinated aryl pyrazole **AM251** (**105b**) in 96 % purity\* (Scheme 3.4.10).



**Scheme 3.4.10.** Sequential preparation/purification of iodinated rimonabant analogue using a Si-based succinimide scavenger **121**.

*Reagents and conditions:* i) NaI, NCS, TFA-HOAc (1:3 v/v), RT, 1 h; ii) EtOH, 80 °C, 1 h; iii) NH<sub>2</sub>NH<sub>2</sub> hydrate, K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C, 24 h.

\* The HPLC chromatogram for pure **AM251** shows three distinct peaks (see Experimental section, Schemes 4.3.1 and 4.3.2.). The relative intensity of these peaks varies depending on the pH of the eluent system used. We presume that these peaks correspond to rotamers about  $\tau_1$  and/or  $\tau_2$  (see Scheme 3.1.2).

The success of this rapid, one-pot functionalisative cleavage and purification protocol augurs well for the development of an efficient procedure to prepare radio-labelled rimonabant analogues for PET and SPECT imaging.

### 3.5 Conclusion

A novel protocol for the parallel preparation of cannabinoid receptor ligands from a functionalised Ge-based resin **119** has been developed. Treatment of this resin with various amines and hydrazines afforded novel resin-bound amide and aryl hydrazide derivatives **120** which upon *ipso*-iododegermylation by NaI/NCS in TFA-HOAc afford the required ligands **105** cleanly and in good yield. A small library of iodinated CB1 ligands was prepared by this protocol which exhibited high performance and reliability.

The succinimide by-product can be removed *in situ* by employing the hydrazine resin **121** to give pure iodinated ligands. This proof-of-concept protocol should be readily applied in the preparation of radio-labelled ligands for *in vivo* studies.

### 3.6 Future work

It remains to further optimise the *ipso*-iododegermylation process to reduce the reaction time and to prepare a wider array of derivatives for evaluation. In addition, It is envisioned to employ radio NaI ( $\text{Na}^{123}\text{I}$  or  $\text{Na}^{124}\text{I}$ ) for the cleavage and explore the efficiency of the resulting radio-ligands as imaging reagents.

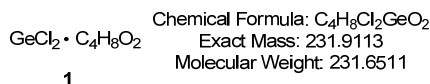
## 4. Experimental section

### 4.1 General directions

**Solvents and reagents:** see the appendixes 1 and 2. **Chromatography:** Flash chromatography (FC) was carried out on Silica gel (BDH Silica gel for flash chromatography) according to the method described by Still,<sup>230</sup> or by using either Isolute Flash Silica (1 g, 5 g, 50 g). TLC was performed on aluminium backed silica gel plates (Merck Silica gel 60 F<sub>254</sub>) which were developed with UV fluorescence (254 nm and 365 nm) and KMnO<sub>4</sub>(aq)/Δ. **<sup>1</sup>H NMR spectra:** These were recorded at 270, 400 or 500 MHz on Jeol 270 GSX, Bruker-DRX 400, AV-400 or AV-500 instruments respectively. Chemical shifts (δ<sub>H</sub>) are given in parts per million (ppm) as referenced to the appropriate residual solvent peak. Broad signals are assigned as br. All spectra were compared with reference spectra of authentic products and reagents. **<sup>13</sup>C NMR spectra:** These were recorded at 100.6 MHz on Bruker AV-400 instrument or at 125.1 MHz on a Bruker AV-500 instrument. Chemical shifts (δ<sub>C</sub>) are given in parts per million (ppm) as referenced to CHCl<sub>3</sub>, and are assigned as s, d, t, and q, for C, CH, CH<sub>2</sub>, and CH<sub>3</sub> respectively. The <sup>13</sup>C signals for the R<sub>f</sub>-tag were assigned by running a partially <sup>13</sup>C{<sup>19</sup>F} decoupled spectrum in the case of R<sub>f</sub>-tagged germanes (see Appendix 3, A 3.3). **<sup>19</sup>F NMR spectra:** These were recorded at 376 MHz on Bruker-DRX 400, AV-400 instruments respectively. Chemical shifts (δ<sub>F</sub>) are given in parts per million (ppm) as referenced to CCl<sub>3</sub>F. **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 <sup>74</sup>Ge, <sup>35</sup>Cl and <sup>79</sup>Br isotopes. HRMS values are valid to ±5ppm. **GC/MS:** Analyses were carried out using a Trio-1 with HP 5890 gas chromatograph. **Isomeric ratio of styrenes:** On the occasions where the geometrical (*E* and *Z*) and regioisomers (α) of styrenes could not be isolated pure, they were identified using <sup>1</sup>H NMR spectroscopic analysis of the mixture and their relative ratio was determined using GC-MS analysis. **Melting points:** Analyses were carried out using a Khofler hot stage and are uncorrected.

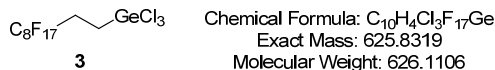
## 4.2 Development of novel aryl- and alkenyl- cross-coupling reactions based on light fluororous-tagged organogermanes

### Germanium(II) chloride 1,4-dioxane complex **1**<sup>231</sup>



A stirred solution of germanium(IV) chloride (37.6 g, 175.3 mmol, 20 mL) and tetramethyldisiloxane (TMDS) (25.08 g, 186.7 mmol, 33 mL) in 1,4-dioxane (50 mL) was heated to 100 °C for 3 h. After cooling to 0 °C, the resulting white precipitates was collected by filtration and washed with cold  $\text{CHCl}_3$  ( $3 \times 20$  mL). After drying under vacuum, dichlorogermylene·1,4-dioxane complex **1** was obtained as white needles (35.3, 87 %).

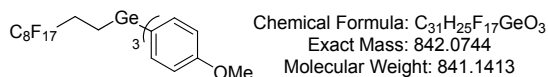
### Trichloro-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodecyl)germane **3**<sup>121</sup>



*1H,1H,2H,2H-Perfluorodecyl iodide 2* (12.5 g, 41.56 mmol) and dichlorogermylene·1,4-dioxane complex **1** (5.00 g, 41.56 mmol) were heated in a Carius tube at 150 °C for 24 h. After cooling to RT, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (500 mL) and added dropwise to  $\text{H}_2\text{O}$  (500 mL). The resulting white precipitate was collected by filtration, washed with  $\text{H}_2\text{O}$  (300 mL) then  $\text{CH}_2\text{Cl}_2$  (300 mL) and dried under suction. The dried precipitate was stirred in conc. HCl (37% w/v) for 16 h and then extracted with  $\text{CH}_2\text{Cl}_2$  ( $5 \times 100$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give trichlorogermane **3** as a brown oil (9.70 g, 78%).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.20 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.47 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ );  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ ):  $\delta$  22.1 (t), 25.0 (t,  $J_{\text{CF}}$  23.0), 108.6 (s), 110.5 (s), 113.5 (s), 114.4 (s), 115.7 (s), 116.9 (s), 117.3 (s), 118.6 (s);  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -126.5 [s, 2F,  $\text{CF}_2(\text{CH}_2)_2$ ], -123.2 (s, 2F), -122.6 (s, 2F), -121.8 (s, 4F,  $4 \times \text{CF}_2$ ), -121.6 (s, 2F), -115.3 (s, 2F), -80.7 [s, 3F,  $\text{CF}_3(\text{CF}_2)_7(\text{CH}_2)_2$ ]; IR  $\nu_{\text{max}}$  (neat) 2930, 1440, 1365, 1245, 905, 825  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{Cl}^+$ )

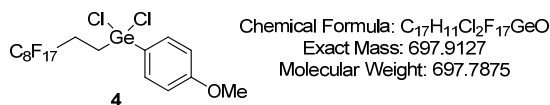
(rel. intensity) 606 [(M-F)<sup>+</sup>, 41], 590 (4), 464 (33), 158 (23), 109 (20).

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)-tris(4-methoxyphenyl)germane<sup>121</sup>**



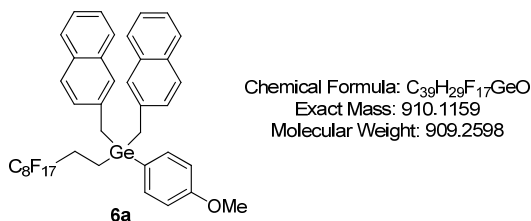
To a solution of trichlorogermane **3** (5.00 g, 6.88 mmol) in THF (15.0 mL) was added a solution of *para*-anisyl methoxyphenylmagnesiumbromide (15.5 mL, 31.0 mmol, 0.5 M). The resulting reaction mixture was stirred at reflux for 3 h. The yellow reaction mixture was cooled to 0 °C before quenching dropwise with methanol until effervescence ceased. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (2 × 20.0 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo*. Sublimation of 4,4'-bismethoxybiphenyl from the residue (100 °C /0.1mmHg using a Kugelrohr) followed by purification by FC (petrol/CH<sub>2</sub>Cl<sub>2</sub> 50/50 → CH<sub>2</sub>Cl<sub>2</sub>) and drying under high vacuum gave *tris-4-anisylgermane* as a white amorphous solid (3.96 g, 70%). mp 55-57 °C; R<sub>f</sub> 0.35 (petrol/CH<sub>2</sub>Cl<sub>2</sub>, 70/30); <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 1.63 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 2.19 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 3.81 (s, 9H, 3 × ArOCH<sub>3</sub>), 6.94 (d, *J* = 8.5 Hz, 6H, ArH), 7.37 (d, *J* = 8.5 Hz, 6H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 3.7 (t), 27.0 (t, *J*<sub>CF</sub> 23.0), 55.0 (3q), 114.0 (6d), 118.9 (3s), 126 (6d), 160.6 (3s), eight carbons not observed; <sup>19</sup>F NMR (376 MHz; CDCl<sub>3</sub>): δ -126.3 (s, 2F), -123.2 (s, 2F), -122.7 (s, 2F), -122.1 (s, 4F, 2 × CF<sub>2</sub>), -121.9 (s, 2F), -115.3 (s, 2F), -80.8 [s, 3F, CF<sub>3</sub>(CF<sub>2</sub>)<sub>7</sub>(CH<sub>2</sub>)<sub>2</sub>]; IR ν<sub>max</sub> (neat) 3020, 1440, 1365, 1245, 900, 835 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) (rel. intensity) 841 (M<sup>+</sup>, 9), 735 (42), 715 (24), 395 (100); HRMS (EI<sup>+</sup>) calc'd. for C<sub>31</sub>H<sub>24</sub><sup>74</sup>GeO<sub>3</sub>F<sub>17</sub> 842.0744, found 842.0721 (Δ 2.7 ppm).

**Dichloro-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodecyl)-(4-methoxyphenyl)germane **4****<sup>121</sup>



To a solution of *tris-para*-anisylgermane (5.00 g, 5.944 mmol) in 1,4 dioxane (5.00 mL) was added a solution of HCl (60.0 mL, 240 mmol, 4.0 M). The reaction mixture was stirred for 5 h and the solvent was then removed *in vacuo* to give *dichlorogermane 4* as a white amorphous solid (3.60 g, 87%). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 1.95 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 2.45 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 3.81 (s, 3H, ArOCH<sub>3</sub>), 6.92 (d, *J* = 8.5 Hz, 2H, ArH), 7.35 (d, *J* = 8.5 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 15.3 (t), 25.4 (t, *J*<sub>CF</sub> = 23.0 Hz), 55.3 (q), 108.2 (s), 110.1 (s), 113.0 (s), 114.2 (s), 114.8 (2d), 115.7 (s), 116.6 (s), 117.1 (s), 118.0 (s), 125.1 (s), 133.7 (2d) 162.7 (s); <sup>19</sup>F NMR (376 MHz; CDCl<sub>3</sub>): δ -126.2 (s, 2F), -123.3 (s, 2F), -122.7 (s, 2F), -122.1 (s, 4F, 2 × CF<sub>2</sub>), -121.9 (s, 2F), -115.4 (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>], -80.8 (t, 3F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>); IR ν<sub>max</sub> (KBr) 3035, 2975, 1595, 1505, 1455, 1200, 960, 825 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) (rel. intensity) 698 (M<sup>+</sup>, 47), 663 (4), 295 (12), 251 (100), 235 (16); HRMS (EI<sup>+</sup>) calc'd. for C<sub>17</sub>H<sub>11</sub><sup>74</sup>GeOCl<sub>2</sub>F<sub>17</sub> 697.9127, found 697.9125 (Δ 0.3 ppm).

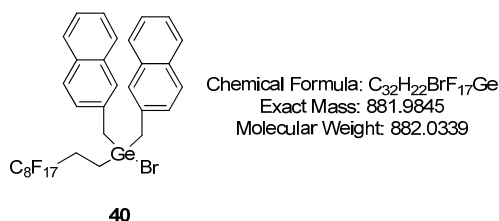
**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)-(4-methoxyphenyl)bis(naphthalen-2-ylmethyl)germane **6a****<sup>121</sup>



To oven dried magnesium turnings (0.704 g, 29.0 mmol) in Et<sub>2</sub>O (25.0 mL) was added 2-bromomethylnaphthalene **5** (5.97 g, 27.0 mmol) to initiate Grignard reagent formation. To this solution was added a solution of dichlorogermane **4** (3.60 g, 5.15 mmol) in Et<sub>2</sub>O (2.00 mL) dropwise and the resulting mixture stirred for 2.5 h. A sat. solution NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred and the solvent was then removed *in vacuo*. The residue taken up in Et<sub>2</sub>O (30.0 mL)

and washed with water ( $2 \times 10.0$  mL) and was dried over  $\text{MgSO}_4$ . 2-methylnaphthalene was sublimed from the residue ( $60$  °C/ $0.1$ mmHg using a Kugelrohr) then bis(2-naphthyl)ethylene was removed from the residue by recrystallisation with  $\text{Et}_2\text{O}$  ( $16.0$  mL) at  $0$  °C, filtration through cotton plug and washed with hexane ( $2 \times 10.0$  mL). Solvents were then removed from the filtrate *in vacuo* and purification by FC (petrol/ $\text{CH}_2\text{Cl}_2$ ,  $95/5 \rightarrow 80/20$ ) gave bis(naphthylmethyl)germane **6a** as a yellow amorphous solid ( $3.35$  g,  $71\%$ ). mp  $189$ - $190$  °C;  $R_f$   $0.30$  (petrol:EtOAc,  $95/5$ );  $^1\text{H}$  NMR ( $400$  MHz;  $\text{CDCl}_3$ ):  $\delta$   $1.16$  (m,  $2\text{H}$ ,  $\text{CH}_2\text{CH}_2\text{Ge}$ ),  $1.87$  (m,  $2\text{H}$ ,  $\text{CH}_2\text{CH}_2\text{Ge}$ ),  $2.73$  (s,  $4\text{H}$ ,  $2 \times \text{GeCH}_2\text{NP}$ ),  $3.85$  (s,  $3\text{H}$ ,  $\text{OCH}_3$ ),  $6.95$  (d,  $J = 6.7$  Hz,  $2\text{H}$ , ArH),  $7.09$  (dd,  $J = 6.7, 1.8$  Hz,  $2\text{H}$ , ArH),  $7.27$  (d,  $J = 6.7$  Hz,  $2\text{H}$ , ArH),  $7.37$  (s,  $2\text{H}$ , ArH),  $7.39$ - $7.47$  (m,  $4\text{H}$ , ArH),  $7.64$  (d,  $J = 7.7$  Hz,  $2\text{H}$ , ArH),  $7.70$  (d,  $J = 8.4$  Hz,  $2\text{H}$ , ArH),  $7.80$  (d,  $J = 7.7$  Hz,  $2\text{H}$ , ArH);  $^{13}\text{C}$  NMR ( $100.7$  MHz;  $\text{CDCl}_3$ )  $\delta$   $2.2$  (t),  $22.8$  (t,  $J_{\text{CF}} = 23.0$  Hz),  $26.4$  (2t),  $55.0$  (q),  $108.4$  (s),  $110.2$  (s),  $110.7$  (2s),  $111.02$  (s),  $113.4$  (s),  $114.2$  (2d),  $115.0$  (s),  $118.1$  (s),  $124.8$  (2d),  $125.8$  (2d),  $126.0$  (2d),  $127.0$  (2d),  $127.4$  (2d),  $127.6$  (2d),  $128.0$  (2d),  $131.3$  (2s),  $133.8$  (2s),  $135.1$  (2d),  $136.7$  (3s),  $160.6$  (s);  $^{19}\text{F}$  NMR ( $376$  MHz;  $\text{CDCl}_3$ ):  $\delta$   $-125.2$  (s,  $2\text{F}$ ),  $-122.5$  (s,  $2\text{F}$ ),  $-121.7$  (s,  $2\text{F}$ ),  $-120.9$  (m,  $6\text{F}$ ),  $-115.4$  [quintet,  $J = 14.8$  Hz,  $2\text{F}$ ,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ],  $-79.8$  (t,  $J = 10.0$  Hz,  $3\text{F}$ ,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ); IR  $\nu_{\text{max}}$  (neat)  $3031, 2925, 1628, 1590, 1422, 1282, 1245, 1200, 1146, 820$   $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity)  $910$  ( $\text{M}^+$ ,  $9$ ),  $769$  ( $89$ ),  $436$  ( $3$ ),  $341$  ( $52$ ),  $141$  ( $100$ ); HRMS ( $\text{EI}^+$ ) calc'd. for  $\text{C}_{39}\text{H}_{29}^{74}\text{GeF}_{17}\text{O}$   $910.1159$ , found  $910.1145$  ( $\Delta$   $1.6$  ppm).

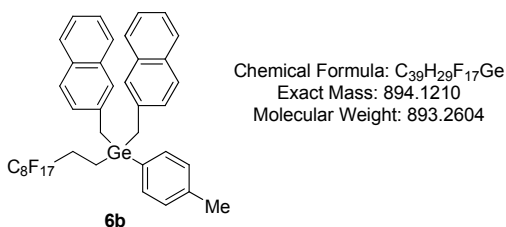
**Bromo-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodecyl)-bis(naphthalen-2-ylmethyl)germane **40****



To a solution of *para*-anisyl germane **6a** ( $0.102$  g,  $0.112$  mmol) in  $\text{CH}_2\text{Cl}_2$  ( $10.0$  mL) was added a solution of conc. HBr ( $2.0$  mL,  $48\%$  wt.). The resulting biphasic reaction mixture was stirred at rt for  $12$  h, extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20.0$  mL). The

combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to give bromogermane **40** as a brown amorphous solid (0.087 g, 88%). mp 172-174 °C;  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.38 (m, 2H,  $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}_2\text{Ge}$ ), 1.93 (m, 2H,  $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.97 (d,  $J = 12.7$  Hz, 2H,  $\text{GeCH}_2\text{NP}$ ), 3.01 (d,  $J = 12.7$  Hz, 2H,  $\text{GeCH}_2\text{NP}$ ), 7.21 (dd,  $J = 6.6, 1.8$  Hz, 2H, ArH), 7.42-7.49 (m, 6H, ArH), 7.68 (dd,  $J = 6.6, 1.8$  Hz, 2H, ArH), 7.76 (d,  $J = 8.4$  Hz, 2H, ArH), 7.81 (dd,  $J = 6.6, 1.8$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  7.5 (t), 26.4 (t,  $J_{\text{CF}} = 23.0$  Hz), 28.3 (2t), 110.2 (s), 110.6 (2s), 110.7 (s), 110.9 (3s), 117.1 (s), 125.4 (2d), 126.3 (2d), 126.4 (2d), 126.9 (2d), 127.1 (2d), 127.7 (2d), 128.5 (2d), 131.7 (2s), 133.6 (2s), 133.7 (2s);  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -125.2 (s, 2F), -122.6 (s, 2F), -121.8 (s, 2F), -121.0 (m, 6F), -115.0 [quintet,  $J = 15.1$  Hz, 2F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ], -79.8 [t,  $J = 9.4$  Hz, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ]; IR  $\nu_{\text{max}}$  (neat) 3055, 2990, 1600, 1420, 1265, 895, 750  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{FAB}^+$ ) (rel. intensity) 882 ( $\text{M}^+$ , 1), 803 (1), 141 (100); HRMS ( $\text{ESI}^+$ ) calc'd. for  $\text{C}_{32}\text{H}_{23}^{79}\text{BrF}_{17}^{74}\text{Ge}$  ( $\text{MH}^+$ ) 882.9924, found 882.9932 ( $\Delta$  1.0 ppm).

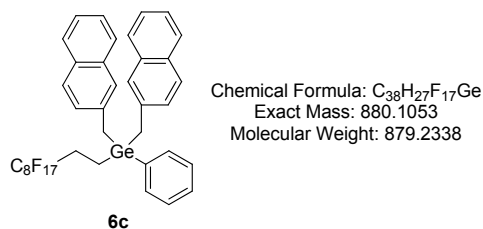
**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl)*para*-tolylgermane 6b**



To a solution of bromogermane **40** (0.800 g, 0.955 mmol), in  $\text{Et}_2\text{O}$  (10.0 mL) at 0 °C was added a solution of *para*-tolylmagnesiumbromide (4.75 mL, 4.75 mmol, 1.0 M) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then at rt for over 14 h. The resulting solution was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and a solution of 1.0 M  $\text{NH}_4\text{Cl}$  was added to the reaction mixture until no effervescence occurred. Following extraction with ( $2 \times 20.0$  mL) of  $\text{Et}_2\text{O}$ , the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to give green oily residue which was purified by FC (hexane/ $\text{EtOAc}$ , 97/3) to give pure 4-tolyl germane **6b** as a brown oil (0.773 g, 87%).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.20 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 1.89 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.45 (s, 3H,  $\text{GeC}_6\text{H}_4\text{CH}_3$ ), 2.76 (s, 4H,  $2 \times \text{GeCH}_2\text{NP}$ ), 7.13 (d, 2H,  $J = 8.4$  Hz, ArH),

7.25 (d, 2H,  $J = 6.8$  Hz, ArH), 7.31 (d, 2H,  $J = 7.6$  Hz, ArH), 7.41–7.50 (m, 6H, ArH), 7.68 (d, 2H,  $J = 7.6$  Hz, ArH), 7.73 (d, 2H,  $J = 8.4$  Hz, ArH), 7.83 (d, 2H,  $J = 7.6$  Hz, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  1.9 (t), 21.4 (q), 22.5 (2t), 26.3 (t,  $J_{\text{CF}}$  23.4 Hz), 108.5 (s), 110.2 (s), 110.69 (2s), 110.72 (s), 111.0 (s), 111.1 (s), 118.0 (s), 124.8 (2d), 125.7 (2d), 126.0 (2d), 127.0 (2d), 127.4 (2d), 127.6 (2d), 128.0 (2d), 129.2 (2d), 131.3 (2s), 132.7 (s), 133.8 (2d+s), 136.7 (3s), 139.2 (s);  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -126.6 (s, 2F), -123.9 (s, 2F), -123.1 (s, 2F), -122.3 (m, 6F), -116.7 [quintet,  $J = 15$  Hz, 2F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ], -81.2 [t,  $J = 10$  Hz, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ]; IR  $\nu_{\text{max}}$  (neat) 3024, 2980, 1600, 1510, 1420, 1265, 895, 745  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 894 ( $\text{M}^+$ , 25), 753 (44), 322 (43), 282 (47), 211 (66), 141 (100); HRMS calc'd. for  $\text{C}_{39}\text{H}_{29}^{74}\text{GeF}_{17}$  894.1209, found 894.1244 ( $\Delta$  3.8 ppm).

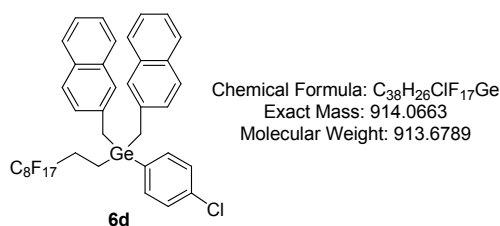
**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl)germane 6c**



To a solution of bromogermane **40** (0.50 g, 0.567 mmol), in THF (10.0 mL) at 0 °C was added a solution of phenylmagnesiumbromide (0.68 mL, 1.7 mmol, 2.5 M) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then at rt for over 14 h. The resulting solution was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and a solution of 1.0 M  $\text{NH}_4\text{Cl}$  was added to the reaction mixture until no effervescence occurred. Following extraction with ( $2 \times 20.0$  mL) of  $\text{Et}_2\text{O}$ , the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to give green oily residue which was purified by FC (hexane/ $\text{EtOAc}$ , 97/3) to give pure *phenylgermane 6c* as a pale yellow oil (0.4122 g, 83 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.19 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 1.89 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.76 (s, 4H,  $2 \times \text{GeCH}_2\text{NP}$ ), 7.09 (dd,  $J = 8.4, 1.2$  Hz, 2H, ArH), 7.73–7.49 (m, 11H, ArH), 7.65 (d,  $J = 7.4$  Hz, 2H, ArH), 7.71 (d,  $J = 8.4$  Hz, 2H,

ArH), 7.81 (d,  $J = 7.4$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  1.9 (t), 22.5 (2t), 26.3 (t,  $J_{\text{CF}}$  23.4 Hz), 108.3 (s), 110.2 (2s), 110.7 (2s), 111.0 (2s), 111.1 (s), 118.0 (s), 124.8 (2d), 125.7 (2d), 126.1 (2d), 127.0 (2d+s), 127.4 (2d), 127.6 (2d), 128.1 (2d), 128.4 (2d), 129.3 (d), 131.3 (2s), 133.7 (2s), 133.8 (2d), 136.5 (2s);  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -125.2 (s, 2F), -122.6 (s, 2F), -121.8 (s, 2F), -121.0 (m, 6F), -115.4 [quintet,  $J = 14.7$  Hz, 2F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ], -79.8 [t,  $J = 9.7$  Hz, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ]; IR  $\nu_{\text{max}}$  (neat) 3030, 2985, 1600, 1415, 1265, 895, 750  $\text{cm}^{-1}$ ;  $m/z$  (FAB $^+$ ) (rel. intensity) 739 [(M-NpCH $_2$ ) $^+$ , 2], 459 (1), 141 (100); HRMS (FAB $^+$ ) calc'd. for  $\text{C}_{27}\text{H}_{18}\text{F}_{17}^{74}\text{Ge}$  [(M-NapCH $_2$ ) $^+$ ] 739.0845, found 739.0870 ( $\Delta$  3.4 ppm).

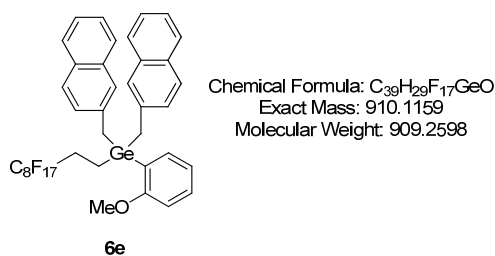
**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(naphthalen-2-ylmethyl)(4-chlorophenyl)germane 6d**



To a solution of 4-chloro-1-bromoenzene (0.4038 g, 2.10 mmol) in THF (10.0 mL) at  $-78$   $^{\circ}\text{C}$  was added a solution of  $t\text{BuLi}$  (3.3 mL, 4.62 mmol, 1.4M in pentane) dropwise resulting in a yellow solution. The solution was stirred at  $-78$   $^{\circ}\text{C}$  for 30 min to achieve lithium-halogen exchange. The resulting solution mixture was added bromogermane **40** (0.62 g, 0.703 mmol) at  $-78$   $^{\circ}\text{C}$  and stirred for 1 h than warming to RT for 16 h. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and a solution of 1.0 M  $\text{NH}_4\text{Cl}$  was added to the reaction mixture until no effervescence occurred. Following extraction with ( $2 \times 20.0$  mL) of  $\text{Et}_2\text{O}$ , the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to give green oily residue which was purified by FC (hexane/ $\text{EtOAc}$ , 97/3) to give pure (4-chlorophenyl)germane **6d** as a pale yellow oil (0.514 g, 80 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.20 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 1.84 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.74 (s, 4H,  $2 \times \text{GeCH}_2\text{NP}$ ), 7.07 (dd,  $J = 6.7, 1.7$  Hz, 2H, ArH), 7.25 (d,  $J = 8.2$  Hz, 2H, ArH), 7.36 (d,  $J = 7.7$  Hz, 2H, ArH), 7.42-7.49 (m, 6H, ArH), 7.66 (d,  $J = 7.7$  Hz, 2H, ArH), 7.71 (d,  $J = 8.2$  Hz, 2H, ArH), 7.81 (d,  $J = 7.7$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  1.8 (t), 22.4 (2t),

26.2 (t,  $J_{CF} = 23.5$  Hz), 108.3 (s), 110.2 (s), 110.7 (3s), 110.97 (s), 111.01 (s), 117.9 (s), 125.0 (2d), 125.7 (2d), 126.2 (2d), 127.0 (2d), 127.2 (2d), 127.6 (2d), 128.2 (2d), 128.6 (2d), 131.3 (2s), 133.7 (2s), 134.7 (s), 135.1 (2d), 135.7 (s), 136.1 (2s);  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -125.2 (s, 2F), -122.5 (s, 2F), -121.8 (s, 2F), -121.0 (m, 6F), -115.4 [quintet,  $J = 15$  Hz, 2F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ], -79.8 [t,  $J = 10$  Hz, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ]; IR  $\nu_{\text{max}}$  (neat) 3050, 2980, 1595, 1405, 1265, 1090, 895, 750  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{FAB}^+$ ) (rel. intensity) 773  $[(\text{M-NpCH}_2)^+, 1]$ , 429 (1), 401 (2), 141 (100); HRMS ( $\text{FAB}^+$ ) calc'd. for  $\text{C}_{27}\text{H}_{17}^{35}\text{ClF}_{17}^{74}\text{Ge}$   $[(\text{M-NapCH}_2)^+]$  772.9954, found 772.9952 ( $\Delta$  -0.2 ppm).

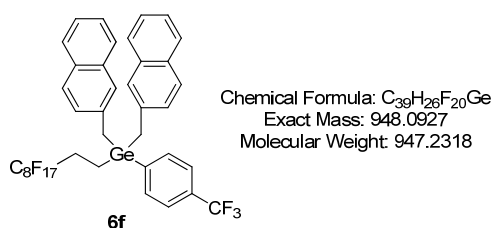
**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl)(2-methoxyphenyl)germane 6e**



To a solution of 2-methoxy-1-bromobenzene (0.3324 g, 1.78 mmol) in THF (10.0 mL) at  $-78^\circ\text{C}$  was added a solution of  $t\text{-BuLi}$  (2.6 mL, 3.64 mmol, 1.4M in pentane) dropwise resulting in a yellow solution. The solution was stirred at  $-78^\circ\text{C}$  for 30 min to achieve lithium-halogen exchange. The resulting solution mixture was added bromogermane **40** (0.5234 g, 0.593 mmol) at  $-78^\circ\text{C}$  and stirred for 1 h than warmed up to RT for 16 h. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and a solution of 1.0 M  $\text{NH}_4\text{Cl}$  was added to the reaction mixture until no effervescence occurred. Following extraction with ( $2 \times 20.0$  mL) of  $\text{Et}_2\text{O}$ , the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to give green oily residue which was purified by FC (hexane/ $\text{EtOAc}$ , 95/5) to give pure (2-methoxyphenyl)germane **6e** as a pale yellow oil (0.4706 g, 87 %);  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.19 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 1.89 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.78 (s, 4H,  $2 \times \text{GeCH}_2\text{NP}$ ), 3.69 (s, 3H,  $\text{OCH}_3$ ), 6.89 (d,  $J = 8.4$  Hz, 1H, ArH), 7.02 (t,  $J = 7.2$  Hz, 1H, ArH), 7.10 (d,  $J = 8.4$  Hz, 2H, ArH), 7.34-7.39 (m, 3H, ArH), 7.40-7.46 (m, 5H, ArH), 7.62 (d,  $J = 8.0$  Hz, 2H, ArH), 7.68 (d,  $J = 8.4$  Hz, 2H, ArH), 7.79 (d,  $J = 7.7$

Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  2.7 (t), 22.7 (2t), 26.6 (t,  $J_{\text{CF}}$  23.2 Hz), 54.7 (q), 108.4 (s), 110.2 (s), 110.7 (2s), 109.6 (2d), 111.0 (2s), 111.1 (s), 118.2 (s), 121.0 (2d), 124.5 (s), 124.6 (2d), 125.7 (2d), 125.9 (2d), 127.0 (2d), 127.5 (2d+s), 127.8 (2d), 131.1 (d), 131.2 (s), 133.7 (2s), 134.9 (d), 137.3 (2s), 162.8 (s);  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -125.1 (s, 2F), -122.6 (s, 2F), -121.8 (s, 2F), -121.0 (m, 6F), -115.3 [quintet,  $J$  = 14.7 Hz, 2F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ], -79.8 [t,  $J$  = 9.8 Hz, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ]; IR  $\nu_{\text{max}}$  (neat) 3030, 2980, 1595, 1510, 1410, 1265, 895, 750  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{FAB}^+$ ) (rel. intensity) 769  $[(\text{M-NpCH}_2)^+$ , 1], 463 (1), 341 (5), 141 (100); HRMS ( $\text{FAB}^+$ ) calc'd. for  $\text{C}_{28}\text{H}_{20}\text{F}_{17}^{74}\text{GeO}$   $[(\text{M-NapCH}_2)^+]$  765.0480, found 765.0480 ( $\Delta$  0 ppm).

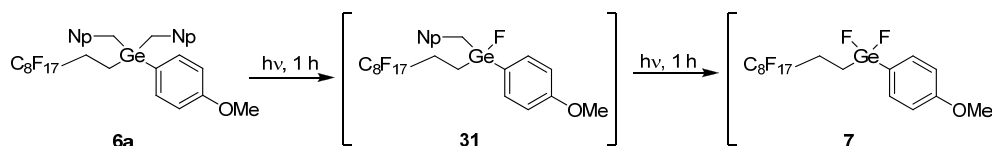
**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl)(4-trifluoromethylphenyl)germane 6f<sup>121</sup>**



To oven dried magnesium turnings (0.032 g, 1.34 mmol) in THF (33.0 mL) was added *para*-trifluoromethylbromobenzene (1.23 g, 1.23 mL, 1.34 mmol) and the reaction mixture was stirred for 2 h to initiate Grignard reagent formation. To the resulting orange coloured reaction mixture was added a solution of a solution of bromogermane **40** (0.500 g, 0.567 mmol) in THF (2.00 mL) dropwise and the reaction mixture was stirred for 4 h. A sat. solution of  $\text{NH}_4\text{Cl}$  was added to the reaction mixture until no effervescence occurred and the reaction mixture was partitioned between  $\text{Et}_2\text{O}$  (40.0 mL) and water (10.0 mL), extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10.0$  mL) and dried over  $\text{MgSO}_4$ . Purification by FC on silica (petrol  $\rightarrow$  petrol/ $\text{EtOAc}$ , 95/5) gave *4-trifluoromethylphenylgermane 6f* as a colourless oil (0.451 g, 84%).  $R_f$  0.31 (petrol/  $\text{EtOAc}$ , 95/5);  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.21 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 1.83 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.76 (s, 4H,  $2 \times \text{GeCH}_2\text{NP}$ ), 7.06 (dd,  $J$  = 6.6, 1.8 Hz, 2H, ArH), 7.35 (s, 2H, ArH), 7.40-7.48 (m, 6H, ArH), 7.61 (t,  $J$  = 8.7 Hz, 4H, ArH), 7.70 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.79 (d,  $J$  = 7.5 Hz, 2H, ArH);  $^{13}\text{C}$

NMR (101 MHz; CDCl<sub>3</sub>)  $\delta$  1.9 (t), 22.4 (2t), 26.2 (t,  $J_{CF}$  = 22.5 Hz), 108.4 (s), 110.2 (s), 110.64 (2s), 110.67 (s), 110.95 (s), 110.99 (s), 117.9 (s), 124.77 (s), 124.81 (2d), 125.0 (2d), 125.8 (2d), 126.2 (2d), 127.0 (2d), 127.1 (2d), 127.6 (2d), 128.2 (2d), 131.3 (2s), 133.7 (2s), 134.2 (2d), 135.8 (3s); <sup>19</sup>F NMR (376 MHz; CDCl<sub>3</sub>):  $\delta$  -125.2 (s, 2F), -122.6 (s, 2F), -121.8 (s, 2F), -121.0 (m, 6F), -115.4 [quintet,  $J$  = 15.1 Hz, 2F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>], -79.8 [t,  $J$  = 10.0 Hz, 3F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>], -62.0 (s, 3F, ArCF<sub>3</sub>); IR  $\nu_{\max}$  (neat) 3020, 2985, 1595, 1420, 1265, 900, 740 cm<sup>-1</sup>;  $m/z$  (EI<sup>+</sup>) (rel. intensity) 948 (M<sup>+</sup>, 55), 807 (71), 787 (16), 769 (20), 549 (23), 141 (100); HRMS (EI<sup>+</sup>) calc'd. for C<sub>39</sub>H<sub>26</sub><sup>74</sup>GeF<sub>20</sub> 948.0927, found 948.0962 ( $\Delta$  3.7 ppm).

**General method for photoactivation of arylgermanes:**



To a solution of the *arylgermane* (0.076 mmol) in MeCN/MeOH (3/1 v/v, 20 mL) in a Pyrex Schlenk tube (1 mm thick) was added powdered Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O (0.304 mmol). The resulting mixture was purged with argon for 30 min before irradiating using a 125 W high pressure Hg lamp for 1 h. A further portion of powdered Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O (0.304 mmol) was then added and the solution irradiated for a further 1 h. After this time, the solvent was removed *in vacuo*, the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL), washed with water (2 × 8.0 mL) and dried over MgSO<sub>4</sub> to give the crude *difluoroarylgermane*.

The progress of the photolysis can be conveniently monitored by <sup>19</sup>F NMR. For example, for the photolysis of arylgermane **6a**:

The <sup>19</sup>F NMR after 15 min displays a singlet at  $\delta_F$  -202.4 ppm which corresponds to the mono-germyl fluoride *(4-methoxyphenyl)-(naphthalen-2-ylmethyl)germyl fluoride 31*: <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  1.43 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 2.11 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 3.03 (m, 2H, GeCH<sub>2</sub>Nap), 3.84 (s, 3H, OCH<sub>3</sub>), 6.99 (d,  $J$  = 6.7 Hz, 2H, ArH), 7.26 (d,  $J$  = 6.7 Hz, 1H, ArH), 7.40 (d,  $J$  = 6.7 Hz, 2H, ArH), 7.40-7.52 (m, 2H, ArH), 7.59 (s, 1H, ArH), 7.72-7.85 (m, 3H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>)  $\delta$  6.1 (t), 25.1 (t), 26.3 (t), 55.1 (q), 108.7 (s), 110.6 (s), 111.1 (s), 111.1 (s),

111.4 (3s), 114.5 (2d), 118.4 (s), 125.1 (d), 126.27 (d), 126.31 (d), 127.1 (2d), 127.6 (d), 128.5 (d), 131.6 (s), 133.1 (s), 133.7 (s), 134.3 (2d), 161.7 (s), 1  $\times$  (s) carbon signal absent;  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -202.4 (s, GeF), -125.2 (s, 2F), -122.5 (s, 2F), -121.8 (s, 2F), -120.9 (m, 6F), -115.3 [quintet,  $J = 14.8$  Hz, 2F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ], -79.8 (t,  $J = 10.0$  Hz, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ );  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 788 ( $\text{M}^+$ , 1), 530 (70), 281 (70), 57 (100)}.

After 2 h the peak for this mono-germyl fluoride has disappeared and the  $^{19}\text{F}$  NMR displays three singlets at  $\delta_{\text{F}}$  164.3, -163.0, -162.6 ppm which correspond to the difluorogermane and derivatives thereof (see discussion section 2.6.1.2).  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -164.3 (s), -163.0 (s), -162.6 (s), -126.2 (s, 2F), -123.3 (s, 2F), -122.7 (s, 2F), -122.1 (s, 4F, 2  $\times$   $\text{CF}_2$ ), -121.9 (s, 2F), -115.4  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ], -80.8 (t, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ).  $\{m/z$  ( $\text{EI}^+$ ) (rel. intensity) 666 ( $\text{M}^+$ , 1), 410 (25), 328 (30), 149 (60), 57 (100); HRMS ( $\text{EI}^+$ ) calc'd. for  $\text{C}_{17}\text{H}_{11}^{74}\text{GeF}_{19}\text{O}$  ( $\text{M}^+$ ) 665.9718, found 665.9701 ( $\Delta$  2.7 ppm).

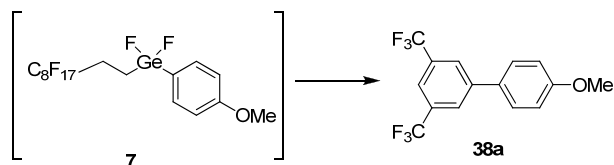
The by-product of the photooxidation, *2-naphthylmethyl methyl ether* **8**, shows the following diagnostic  $^1\text{H}$  NMR signals:  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  3.41 (s, 3H, OMe), 4.62 (s, 2H,  $\text{ArCH}_2$ ), 7.40-7.48 (m, 3H, ArH), 7.75-7.83 (m, 4H, ArH).

If the solution has not been efficiently deoxygenated, some *2-naphthaldehyde* **9** forms and shows the following diagnostic  $^1\text{H}$  NMR signals:  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.55-7.63 (m, 2H, ArH), 7.88-7.96 (m, 4H, ArH), 8.35 (s, 1H, ArH), 10.22 (s, 1H,  $\text{ArCHO}$ );  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 156 ( $\text{M}^+$ , 100), 127 (90), 91(20), 58 (50).

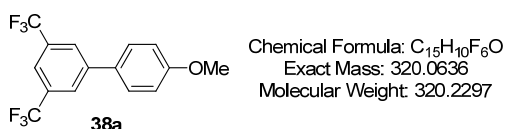
#### *Preparation of difluoro germane 7 by nucleophilic substitution reactions (Scheme 2.6.11)*

To a solution of dichlorogermane **4** (20.2 mg, 0.029 mmol) in  $\text{Et}_2\text{O}$  (5.00 mL) was added of AgF or  $\text{AgBF}_4$  (2.5 eq). The reaction mixture was stirred at RT for 16 h followed by diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and washed with water (2  $\times$  20.0 mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and the solvent was removed *in vacuo*. The crude  $^{19}\text{F}$  NMR spectra indicated essentially identical peaks at  $\delta_{\text{F}}$  -162 ~ -165 ppm as observed following photolysis (as described above).

**General methods for cross-coupling of photoactivated germanes with aryl bromides:**



**4-Methoxy-3',5'-bis-(trifluoromethylbiphenyl) 38a<sup>232</sup>**



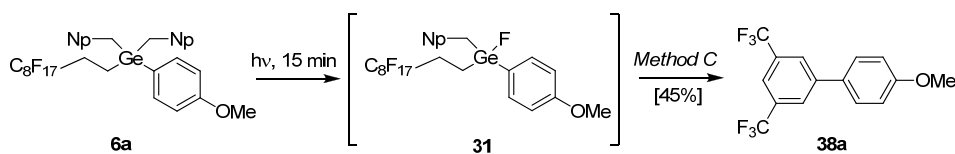
**Method A:** The crude difluoroarylgermane from the photolysis of arylgermane **6a** (113.8 mg, 0.1486 mmol) for 1 h with 4 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$  and powdered potassium fluoride (65.6 mg, 1.13 mmol) were dissolved in DMF (1 mL) and stirred at rt for 1 h.  $\text{PdCl}_2(\text{MeCN})_2$  (4.5 mg, 0.015 mmol) and dppp (9.2 mg, 0.0229 mmol) was dissolved in DMF (2 mL) and stirred at rt for 1 h to give the active catalytic species. The catalyst solution and 3,5-bis(trifluoromethyl)bromobenzene (43.5 mg, 0.1486 mmol, 25.6  $\mu\text{L}$ ) was then added to the difluoroarylgermane solution and the resulting mixture heated at 120 °C for 16 h. The crude reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and washed with water ( $3 \times 10.0$  mL), the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo*. Purification by FC (hexane/ $\text{EtOAc}$ , 97/3) gave 4-methoxy-3',5'-bis-(trifluoromethyl)biphenyl **38a** (25.3 mg, 53 %) as a clear liquid;  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  3.88 (s, 3H,  $\text{OCH}_3$ ), 7.03 (d,  $J = 8.8$  Hz, 2H, ArH), 7.55 (d,  $J = 8.8$  Hz, 2H, ArH), 7.81 (s, 1H, ArH), 7.91 (s, 2H, ArH).  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -62.8 (s, 6F,  $2 \times \text{CF}_3$ ). HRMS calc'd. for  $\text{C}_{15}\text{H}_{10}\text{F}_6\text{O}$  320.0636, found 320.0635 ( $\Delta$  -0.3 ppm).

**Method B:** according for method of Li,<sup>233</sup> the crude difluoroarylgermane from the photolysis of arylgermane **6a** (56.6 mg, 0.074 mmol) for 1 h with 4 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$  and TBAF (70 mg, 0.22 mmol) were dissolved in degassed DMF (2 mL) and stirred for 30 min.  $\text{PdCl}_2(\text{MeCN})_2$  (1.9 mg, 0.007 mmol) and  $\text{P}(2\text{-Tol})_3$  (3.2 mg, 0.0105 mmol) was dissolved degassed DMF (1 mL) for 30 min to give the active catalytic species. The catalyst solution was added to the difluoroarylgermane solution followed by adding 3,5-bis(trifluoromethyl)bromobenzene (43.4 mg, 0.148 mmol,

25.5  $\mu\text{L}$ ) and heated at 120  $^{\circ}\text{C}$  for 16 h under nitrogen atmosphere. The resulting solution was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and washed with water ( $3 \times 10.0$  mL), the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo*. Purification by FC (hexane/ $\text{EtOAc}$ , 97/3) gave *biphenyl* **38a** (14.2 mg, 60 %). Analytical data as shown above.

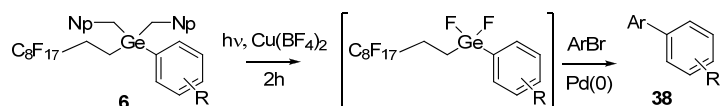
**Method C:** The crude difluoroarylgermane from the photolysis of arylgermane **6a** (47.0 mg, 0.07 mmol) for 1 h with 4 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$  and TBAF (60 mg, 0.19 mmol) was dissolved in degassed DMF (2 mL) and stirred for 30 min.  $\text{PdCl}_2(\text{MeCN})_2$  (2 mg, 0.007 mmol) and  $\text{P}(2\text{-Tol})_3$  (3.6 mg, 0.0105 mmol) were dissolved degassed DMF (1 mL) for 30 min the active catalytic species. The catalyst solution was added to the difluoroarylgermane solution followed by adding 3,5-bis(trifluoromethyl)- bromobenzene (37.3 mg, 0.14 mmol, 22  $\mu\text{L}$ ) and  $\text{CuI}$  ( 14 mg, 0.07 mmol). The resulting mixture heated at 120  $^{\circ}\text{C}$  for 16 h under nitrogen atmosphere. The crude reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and washed with water ( $3 \times 10.0$  mL), the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo*. Purification by FC (hexane/ $\text{EtOAc}$ , 97/3) gave *biphenyl* **38a** (15.2 mg, 68 %). Analytical data as shown above.

*Cross-coupling of mono-fluoro arylgermane 31 with 3,5-bis(trifluoromethyl)-bromobenzene*



Using *method C*, the crude mono-fluoro arylgermane from the photolysis of arylgermane **6a** ( 55.0 mg, 0.083 mmol) for 15 min, TBAF (78.2 mg, 0.248 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (2.2 mg , 0.0083 mmol),  $\text{P}(2\text{-Tol})_3$  (3.8 mg, 0.0125mmol), 3,5-bis(trifluoromethyl)bromobenzene (48.6 mg, 0.166 mmol) and  $\text{CuI}$  ( 16.6 mg, 0.083 mmol) were employed. Purification by FC (hexane/ $\text{EtOAc}$ , 97/3) gave *biphenyl* **38a** (11.9 mg, 45 %). Analytical data as shown above.

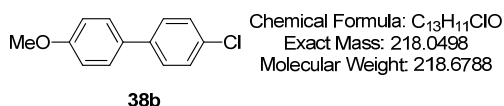
### The scope of aryl germyl-Stille cross-coupling reactions



#### Table 2.6.3, entry 1: 4-Methoxy-3',5'-bis-(trifluoromethylbiphenyl) 38a

Using *method C*, the crude di-fluoro arylgermane (54.6 mg, 0.082 mmol) from the photolysis of arylgermane **6a** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (77.5 mg, 0.246 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (2.1 mg, 0.0082 mmol),  $\text{P}(2\text{-Tol})_3$  (3.7 mg, 0.0123 mmol), 3,5-bis(trifluoromethyl)-bromobenzene (48.1 mg, 0.164 mmol) and  $\text{CuI}$  (16.6 mg, 0.083 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave biphenyl **38a** (11.9 mg, 96 %) \*. Analytical data as shown above.

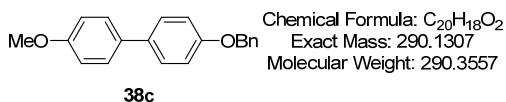
#### Table 2.6.3, entry 2: 4-Chloro-4'-methoxybiphenyl 38b<sup>234</sup>



Using *method C*, the crude difluoroarylgermane (54.6 mg, 0.082 mmol) from the photolysis of arylgermane **6a** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (77.5 mg, 0.246 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (2.1 mg, 0.0082 mmol),  $\text{P}(2\text{-Tol})_3$  (3.7 mg, 0.0123 mmol), 4-chloro-bromobenzene (31.3 mg, 0.164 mmol) and  $\text{CuI}$  (16.4 mg, 0.082 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave 4-chloro-4'-methoxybiphenyl **38b** as a pale yellow oil (15.3 mg, 85 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  3.85 (s, 3H,  $\text{OCH}_3$ ), 6.96-6.99 (m, 2H, ArH), 7.37-7.39 (m, 2H, ArH), 7.46-7.51 (m, 4H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  55.3 (q), 114.3 (2d), 127.9 (2d), 128.0 (2d), 128.8 (2d), 132.4 (s), 132.6 (s), 139.2 (s), 159.2 (s); HRMS calc'd. for  $\text{C}_{13}\text{H}_{11}\text{ClO}$  218.0498, found 218.0499 ( $\Delta$  0.3 ppm).

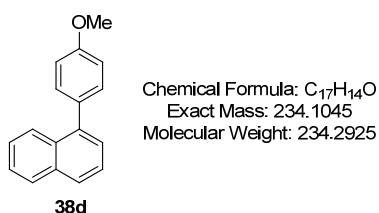
\* The significantly increased yield in this experiment (96 %) as compared to the one on the previous page also using *Method C* (68 %) reflects the longer photolysis period with more  $\text{Cu}(\text{BF}_4)_2$  (see Scheme 2.6.13)

Table 2.6.3, entry 3: **4-Methoxy-4'-(phenylmethoxy)biphenyl 38c**



Using *method C*, the crude difluoroarylgermane (63.7 mg, 0.096 mmol) from the photolysis of arylgermane **6a** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (92.5 mg, 0.294 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.5 mg, 0.0096 mmol), P(2-Tol)<sub>3</sub> (4.4 mg, 0.014 mmol), 1-((4-bromophenoxy)-methyl)benzene (51.5 mg, 0.196 mmol) and CuI (18.6 mg, 0.093 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *4-methoxy-4'-(phenylmethoxy)biphenyl 38c* as a pale yellow oil (18.1 mg, 65 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 3.85 (s, 3H, OCH<sub>3</sub>), 5.11 (s, 2H, ArOCH<sub>2</sub>Ph), 6.97 (d, *J* = 8.6 Hz, 2H, ArH), 7.04 (d, *J* = 8.6 Hz, 2H, ArH), 7.32-7.36 (m, 1H, ArH), 7.41 (t, *J* = 7.4 Hz, 2H, ArH), 7.46-7.50 (m, 6H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 55.3 (q), 70.1 (t), 114.2 (d), 115.1 (3d), 127.5 (2d), 127.8 (4d), 128.0 (d), 128.6 (2d), 133.4 (s), 133.7 (s), 137.0 (s), 157.9 (s), 158.7 (s); IR ν<sub>max</sub> (neat) 3027 (C-H), 2988 (C-H), 1567 (C=C), 980, 870 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) (rel. intensity) 290 (M<sup>+</sup>, 60), 199 (100), 149 (35), 91 (60); HRMS calc'd. for C<sub>20</sub>H<sub>18</sub>O<sub>2</sub> 290.1307, found 290.1303 (Δ -1.3 ppm).

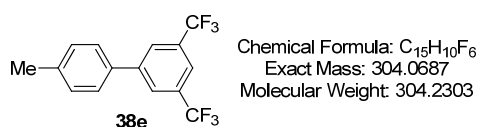
Table 2.6.3, entry 4: **1-(4-Methoxyphenyl)naphthalene 38d**<sup>233</sup>



Using *method C*, the crude difluoroarylgermane (137.0 mg, 0.206 mmol) from the photolysis of arylgermane **6a** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (189.9 mg, 0.603 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (5.3 mg, 0.0206 mmol), P(2-Tol)<sub>3</sub> (9.4 mg, 0.0308 mmol), 1-bromonaphthalene (83 mg, 0.401 mmol, 55.9 μL) and CuI (40.1 mg, 0.201 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *1-(4-methoxyphenyl)naphthalene 38d* as a pale yellow oil (35.7 mg, 74 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 3.90 (s, 3H, OCH<sub>3</sub>), 7.04 (d, *J* = 8.6 Hz, 2H, ArH), 7.40-7.46

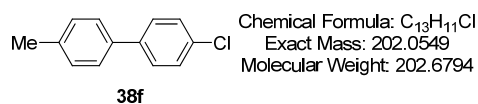
(m, 4H, ArH), 7.47-7.54 (m, 2H, ArH), 7.84 (d,  $J = 8.2$  Hz, 1H, ArH), 7.92 (d,  $J = 9.2$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  55.3 (q), 113.7 (2d), 125.4 (d), 125.7 (d), 125.9 (d), 126.0 (d), 126.9 (d), 127.3 (d), 128.2 (d), 131.1 (2d), 131.8 (s), 133.1 (s), 133.8 (s), 139.9 (s), 158.9 (s); HRMS calc'd. for  $\text{C}_{17}\text{H}_{14}\text{O}$  234.1045, found 234.1041 ( $\Delta$  -1.6 ppm).

Table 2.6.3, entry 5: **4-Methyl-3',5'-bis-(trifluoromethyl)biphenyl 38e**<sup>235</sup>



Using *method C*, the crude difluoroarylgermane (95.6 mg, 0.147 mmol) from the photolysis of arylgermane **6b** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (137.6 mg, 0.437 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (3.8 mg, 0.0146 mmol),  $\text{P}(2\text{-Tol})_3$  (6.6 mg, 0.0217 mmol), 3,5-bis(trifluoromethyl)-bromobenzene (85.3 mg, 0.291 mmol, 50.2  $\mu\text{L}$ ) and  $\text{CuI}$  (29.1 mg, 0.146 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *4-methyl-3',5'-bis-(trifluoromethyl)biphenyl 38e* as a pale yellow (37.4 mg, 60 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.43 (s, 3H,  $\text{ArCH}_3$ ), 7.31 (d,  $J = 8.0$  Hz, 2H, ArH), 7.51 (d,  $J = 8.0$  Hz, 2H, ArH), 7.82 (s, 1H, ArH), 7.99 (s, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  21.2 (q), 120.6 (2s), 122.1 (d), 126.9 (2d), 127.0 (2d), 130.0 (2d), 131.8 (s), 132.2 (s), 135.3 (s), 139.0 (s), 143.2 (s); HRMS calc'd. for  $\text{C}_{15}\text{H}_{10}\text{F}_6$  304.0687, found 304.0681 ( $\Delta$  -1.9 ppm)

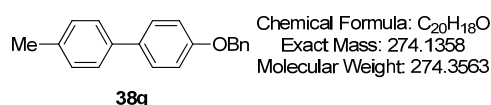
Table 2.6.3, entry 6: **4-Chloro-4'-methylbiphenyl 38f**<sup>236</sup>



Using *method C*, the crude difluoroarylgermane (72.8mg, 0.115 mmol) from the photolysis of arylgermane **6b** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (108.4 mg, 0.344 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (3.0 mg, 0.0116 mmol),  $\text{P}(2\text{-Tol})_3$  (5.7 mg, 0.0173 mmol), 4-chloro-bromobenzene (43.9mg, 0.229 mmol) and  $\text{CuI}$  (22.9 mg, 0.115 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave

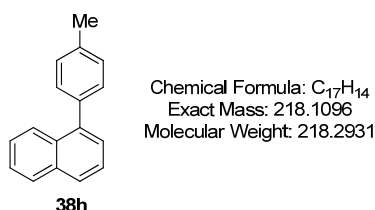
*4-chloro-4'-methylbiphenyl* **38f** as a pale yellow oil (15.9 mg, 69 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.40 (s, 3H,  $\text{ArCH}_3$ ), 7.24 (s, 1H, ArH), 7.37-7.40 (m, 2H, ArH), 7.41-7.48 (m, 3H, ArH), 7.49-7.52 (m, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  21.1 (q), 126.8 (2d), 128.17 (2d), 128.21 (d), 128.8 (d), 129.0 (d), 129.6 (d), 133.0 (s), 137.1 (s), 137.4 (s), 139.6 (s); HRMS calc'd. for  $\text{C}_{13}\text{H}_{11}\text{Cl}$  202.0549, found 202.0557 ( $\Delta$  3.8 ppm).

Table 2.6.3, entry 7: **4-Methyl-4'-(phenylmethoxy)biphenyl 38g**



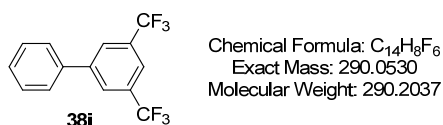
Using *method C*, the crude difluoroarylgermane (82.3 mg, 0.127 mmol) from the photolysis of arylgermane **6b** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (120 mg, 0.381 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (3.3 mg, 0.0127 mmol),  $\text{P}(2\text{-Tol})_3$  (5.8 mg, 0.0191 mmol), 1-((4-bromophenoxy)methyl)benzene (78.5 mg, 0.298 mmol) and  $\text{CuI}$  (25.5 mg, 0.128 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *4-methyl-4'-(phenylmethoxy)biphenyl* **38g** as a pale yellow (16.9 mg, 48 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.38 (s, 3H,  $\text{ArCH}_3$ ), 5.11 (s, 2H,  $\text{ArOCH}_2\text{Ph}$ ), 7.04 (d,  $J = 8.7$  Hz, 2H, ArH), 7.22 (d,  $J = 8.0$  Hz, 2H, ArH), 7.30-7.36 (m, 1H, ArH), 7.38-7.42 (m, 2H, ArH), 7.43-7.47 (m, 4H, ArH), 7.51 (d,  $J = 8.7$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  21.1 (q), 70.1 (t), 115.1 (2d), 126.6 (2d), 127.5 (2d), 128.0 (3d), 128.6 (2d), 129.4 (2d), 134.0 (s), 136.4 (s), 137.0 (s), 137.9 (s), 158.1 (s); IR  $\nu_{\text{max}}$  (neat) 3025, 2850, 1530, 900, 750  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 274 ( $\text{M}^+$ , 30), 183 (20), 141 (25), 91 (100); HRMS calc'd. for  $\text{C}_{20}\text{H}_{18}\text{O}$  274.1358, found 274.1359 ( $\Delta$  0.5 ppm).

Table 2.6.3, entry 8: **1-(4-Methylphenyl)naphthalene 38h**<sup>237</sup>



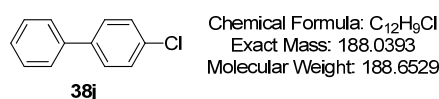
Using *method C*, the crude difluoroarylgermane (119 mg, 0.183 mmol) from the photolysis of arylgermane **6b** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (176mg, 0.559 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (4.7 mg, 0.0181 mmol), P(2-Tol)<sub>3</sub> (8.3 mg, 0.0272 mmol), 1-bromonaphthalene (77.4 mg, 0.373 mmol, 52  $\mu$ L) and CuI (37.1 mg, 0.186 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *1-(4-methylphenyl)naphthalene* **38h** as a pale yellow oil (28.3 mg, 71 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  2.47 (s, 3H, ArCH<sub>3</sub>), 7.32 (d, *J* = 7.9 Hz, 2H, ArH), 7.40-7.48 (m, 4H, ArH), 7.49-7.55 (m, 2H, ArH), 7.86 (d, *J* = 8.2 Hz, 1H, ArH), 7.93 (t, *J* = 9.1 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>)  $\delta$  21.2 (q), 125.4 (d), 125.7 (d), 125.9 (d), 126.1 (d), 126.9 (d), 127.4 (d), 128.2 (d), 129.0 (2d), 129.3 (2d), 131.7 (s), 133.8 (s), 136.9 (s), 137.8 (s), 140.2 (s); HRMS calc'd. for C<sub>17</sub>H<sub>14</sub> 218.1096, found 218.1098 ( $\Delta$  1.1 ppm).

Table 2.6.3, entry 9: **3',5'-bis(Trifluoromethyl)biphenyl 38i**<sup>235</sup>



Using *method C*, the crude difluoroarylgermane (70.3 mg, 0.111 mmol) from the photolysis of arylgermane **6c** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (104.6 mg, 0.332 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.9 mg, 0.0111 mmol), P(2-Tol)<sub>3</sub> (5.1 mg, 0.0167 mmol), 3,5-bis(trifluoromethyl)bromobenzene (64.9 mg, 0.222 mmol, 38.2  $\mu$ L) and CuI (22.1 mg, 0.0111 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *3',5'-bis(trifluoromethyl)biphenyl* **38i** as a pale yellow oil (23.7 mg, 74 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  7.45-7.54 (m, 2H, ArH), 7.61-7.63 (m, 1H, ArH), 7.86 (s, 1H, ArH), 8.01 (d, *J* = 10.0 Hz, 2H, ArH), 8.03 (s, 2H, ArH); HRMS calc'd. for C<sub>14</sub>H<sub>8</sub>F<sub>6</sub> 290.0530, found 290.0523 ( $\Delta$  -2.5 ppm).

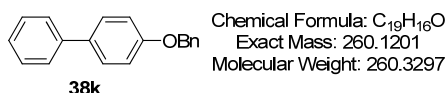
Table 2.6.3, entry 10: **4-Chlorobiphenyl 38j**<sup>238</sup>



Using *method C*, the crude difluoroarylgermane (61 mg, 0.096 mmol) from the

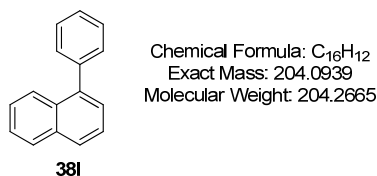
photolysis of arylgermane **6c** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (90.7 mg, 0.288 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.5 mg, 0.0096 mmol), P(2-Tol)<sub>3</sub> (4.4 mg, 0.0145 mmol), 4-chloro-bromobenzene (36.8 mg, 0.192 mmol) and CuI (19.1 mg, 0.096 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *4-chlorobiphenyl* **38j** as a pale oil (11.6 mg, 63 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 7.34-7.40 (m, 1H, ArH), 7.41-7.45 (m, 3H, ArH), 7.47-7.48 (m, 2H), 7.49-7.56 (m, 3H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 127.0 (d), 127.6 (d), 128.2 (2d), 128.4 (d), 128.9 (d), 129.0 (3d), 133.7 (s), 134.6 (s), 136.6 (s); HRMS calc'd. for C<sub>12</sub>H<sub>9</sub>Cl 188.0393, found 188.0385 (Δ -4.1 ppm).

Table 2.6.3, entry 11: **4-(Phenylmethoxy)biphenyl 38k**<sup>233</sup>



Using *method C*, the crude difluoroarylgermane (109.9 mg, 0.173 mmol) from the photolysis of arylgermane **6c** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (163.5 mg, 0.519 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (4.5 mg, 0.0173 mmol), P(2-Tol)<sub>3</sub> (7.9 mg, 0.026 mmol), 1-((4-bromophenoxy)methyl)benzene (91.1 mg, 0.346 mmol) and CuI (34.2 mg, 0.171 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *4-(phenylmethoxy)biphenyl* **38k** as a pale oil (17.8 mg, 40 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 5.12 (s, 2H, ArH), 7.05 (d, *J* = 8.8 Hz, 2H, ArH), 7.30 (t, *J* = 7.3 Hz, 1H, ArH), 7.35 (d, *J* = 7.1 Hz, 1H, ArH), 7.38-7.48 (m, 6H, ArH), 7.51-7.56 (m, 4H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 70.1 (t), 115.1 (2d), 126.67 (d), 126.73 (2d), 127.5 (2d), 128.0 (d), 128.2 (2d), 128.6 (2d), 128.7 (2d), 134.2 (s), 135.7 (s), 140.1 (s), 158.3 (s); HRMS calc'd. for C<sub>19</sub>H<sub>16</sub>O 260.1201, found 260.1190 (Δ -4.3 ppm).

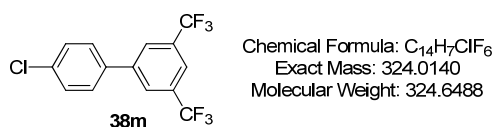
Table 2.6.3, entry 12: **1-Phenylnaphthalene 38l**<sup>237</sup>



Using *method C*, the crude difluoroarylgermane (30.5 mg, 0.048 mmol) from the

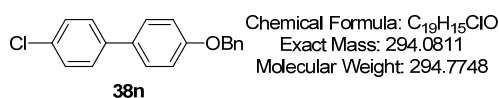
photolysis of arylgermane **6c** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (45.4 mg, 0.144 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (1.2 mg, 0.0046 mmol),  $\text{P}(2\text{-Tol})_3$  (2.1 mg, 0.0069 mmol), 1-bromonaphthalene (20 mg, 0.096 mmol, 13.4  $\mu\text{L}$ ) and  $\text{CuI}$  (9.6 mg, 0.048 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *1-phenylnaphthalene* **38l** as a pale yellow oil (5.8 mg, 60 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.41-7.45 (m, 3H, ArH), 7.47-7.55 (m, 6H, ArH), 7.86 (d,  $J = 8.0$  Hz, 1H, ArH), 7.91 (dd,  $J = 8.0, 3.1$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  125.4 (d), 125.8 (d), 126.0 (2d), 126.9 (d), 127.2 (d), 127.6 (d), 128.2 (3d), 130.1 (2d), 130.2 (s), 133.8 (s), 140.2 (s), 140.7 (s); HRMS calc'd. for  $\text{C}_{16}\text{H}_{12}$  204.0903, found 204.0903 ( $\Delta$  0 ppm).

Table 2.6.3, entry 13: **4-Chloro-3',5'-bis-(trifluoromethyl)biphenyl 38m**<sup>235</sup>



Using *method C*, the crude difluoroarylgermane (34.6 mg, 0.052 mmol) from the photolysis of arylgermane **6d** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (48 mg, 0.152 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (1.3 mg, 0.005 mmol),  $\text{P}(2\text{-Tol})_3$  (2.3 mg, 0.0075 mmol), 3,5-bis(trifluoromethyl)- bromobenzene (30.6 mg, 0.105 mmol, 18  $\mu\text{L}$ ) and  $\text{CuI}$  (10 mg, 0.05 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *4-chloro-3',5'-bis-(trifluoromethyl)biphenyl 38m* as a pale yellow oil (11.9 mg, 71 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.47-7.50 (m, 2H, ArH), 7.51-7.57 (m, 2H, ArH), 7.87 (s, 2H, ArH); HRMS calc'd. for  $\text{C}_{14}\text{H}_7\text{ClF}_6$  324.0140, found 324.0137 ( $\Delta$  -1.1 ppm).

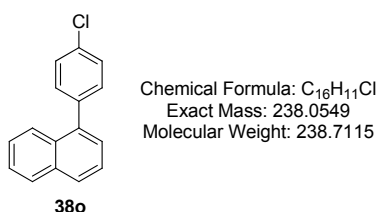
Table 2.6.3, entry 14: **4-Chloro-4'-(phenylmethoxy)biphenyl 38n**



Using *method C*, the crude difluoroarylgermane (50.3 mg, 0.075 mmol) from the photolysis of arylgermane **6d** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (71 mg, 0.225 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (1.9 mg, 0.0073 mmol),  $\text{P}(2\text{-Tol})_3$  (3.3 mg,

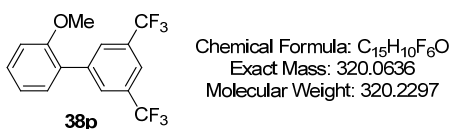
0.011 mmol), 1-((4-bromophenoxy)methyl)- benzene (39.5 mg, 0.150 mmol) and CuI (15 mg, 0.075 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *4-chloro-4'-(phenylmethoxy)biphenyl* **38n** as a pale yellow oil (9.3 mg, 42 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 5.14 (s, 2H, ArOCH<sub>2</sub>Ph), 7.05 (d, *J* = 8.7 Hz, 2H, ArH), 7.31-7.42 (m, 5H, ArH), 7.44-7.50 (m, 6H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 70.1 (t), 115.1 (d), 126.7 (d), 127.5 (d), 127.7 (d), 127.9 (2d), 128.0 (2d), 128.3 (d), 128.6 (d), 128.8 (d), 128.9 (d), 129.1 (d), 132.6 (s), 132.7 (s), 136.8 (s), 139.2 (s), 158.5 (s); IR ν<sub>max</sub> (neat) 3035, 2895, 1550, 870, 740 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) (rel. intensity) 296 [(M<sup>37</sup>Cl)<sup>+</sup>, 30], 294 [(M<sup>35</sup>Cl)<sup>+</sup>, 88], 139 (30), 84 (60), 49 (100); HRMS calc'd. for C<sub>19</sub>H<sub>15</sub>ClO 294.0811, found 294.0807 (Δ -1.5 ppm).

Table 2.6.3, entry 15: **1-(4-Chlorophenyl)naphthalene 38o**<sup>239</sup>



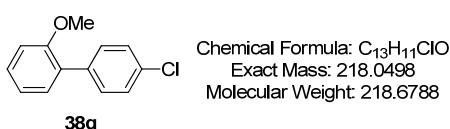
Using *method C*, the crude difluoroarylgermane (79.3 mg, 0.115 mmol) from the photolysis of arylgermane **6d** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (108.6 mg, 0.345 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (3.0 mg, 0.0116 mmol), P(2-Tol)<sub>3</sub> (5.3 mg, 0.017 mmol), 1-bromonaphthalene (47.8 mg, 0.230 mmol, 32.1 μL) and CuI (2.9 mg, 0.115 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *1-(4-chlorophenyl)naphthalene* **38o** as a pale yellow oil (20.6 mg, 75 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 7.39-7.41 (m, 5H, ArH), 7.49-7.55 (m, 3H, ArH), 7.85 (d, *J* = 8.5 Hz, 1H, ArH), 7.88 (d, *J* = 8.3 Hz, 1H, ArH), 7.92 (d, *J* = 7.9 Hz, 1H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 125.3 (d), 125.6 (d), 125.7 (d), 126.2 (d), 126.9 (d), 128.0 (d), 128.3 (d), 128.5 (2d), 130.1 (s), 131.3 (2d), 133.3 (s), 133.8 (s), 138.9 (s), 139.1 (s); HRMS calc'd. for C<sub>16</sub>H<sub>11</sub>Cl 238.0549, found 238.0541 (Δ -3.9 ppm).

Table 2.6.3, entry 16: **2-Methoxy-3',5'-bis-(trifluoromethyl)biphenyl 38p**



Using *method C*, the crude difluoroarylgermane (50.6 mg, 0.076 mmol) from the photolysis of arylgermane **6e** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (71.8 mg, 0.228 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.0 mg, 0.0078 mmol), P(2-Tol)<sub>3</sub> (3.6 mg, 0.012 mmol), 3,5-bis(trifluoromethyl)bromobenzene (44.5 mg, 0.152 mmol, 26.2 μL) and CuI (15.2 mg, 0.076 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *2-methoxy-3',5'-bis-(trifluoromethyl) biphenyl 38p* as a pale yellow oil (15.7 mg, 65 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 3.82 (s, 3H, OCH<sub>3</sub>), 7.02 (d, *J* = 8.3 Hz, 1H, ArH), 7.08 (t, *J* = 7.1 Hz, 1H, ArH), 7.33 (dd, *J* = 7.6, 1.7 Hz, 1H, ArH), 7.41 (td, *J* = 8.3, 1.7 Hz, 1H, ArH), 7.82 (s, 1H, ArH), 7.98 (s, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 55.6 (q), 111.3 (2d), 120.6 (2s), 121.2 (d), 127.5 (s), 129.7 (2d), 130.2 (d), 130.6 (d), 131.0 (2s), 140.5 (s), 156.0 (s); IR ν<sub>max</sub> (neat) 3020, 1605, 1440, 900, 740 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) (rel. intensity) 320 (M<sup>+</sup>, 70), 305 (20), 285 (30), 236 (40), 84 (70), 49 (100); HRMS calc'd. for C<sub>15</sub>H<sub>10</sub>F<sub>6</sub>O 320.0636, found 320.0632 (Δ -1.2 ppm).

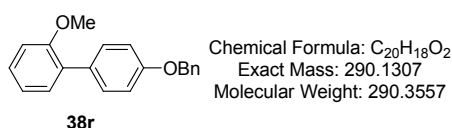
Table 2.6.3, entry 17: **2-Methoxy-4'-chloro-1,1'-biphenyl 38q**<sup>238</sup>



Using *method C*, the crude difluoroarylgermane (95.1 mg, 0.144 mmol) from the photolysis of arylgermane **6e** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (135.3 mg, 0.430 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (3.7 mg, 0.014 mmol), P(2-Tol)<sub>3</sub> (6.6 mg, 0.022 mmol), 4-chloro-bromobenzene (55.1 mg, 0.288 mmol) and CuI (28.7 mg, 0.144 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *2-methoxy-4'-chloro-1,1'-biphenyl 38q* as a pale yellow oil (17.8 mg, 57 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 3.85 (s, 3H, OCH<sub>3</sub>), 7.02 (d, *J* = 8.0 Hz, 1H, ArH), 7.08 (t, *J* = 7.5 Hz, 1H, ArH), 7.30-7.44 (m, 2H, ArH), 7.46 (d, *J* = 8.0 Hz, 2H, ArH), 7.52 (d, *J* = 8.0 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 55.5 (q), 111.2 (2d), 120.9

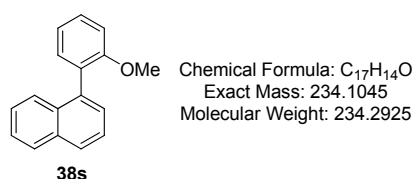
(2s), 121.2 (d), 127.4 (s), 129.6 (2d), 130.4 (d), 130.6 (d), 131.0 (2s), 140.2 (s), 156.3 (s); HRMS calc'd. for  $C_{13}H_{11}ClO$  218.0498, found 218.0496 ( $\Delta$  -0.9 ppm).

Table 2.6.3, entry 18: **2-Methoxy-4'-(phenylmethoxy)biphenyl 38r**



Using *method C*, the crude difluoroarylgermane (132.9 mg, 0.200 mmol) from the photolysis of arylgermane **6e** for 2 h with 8 equivalents of  $Cu(BF_4)_2 \cdot nH_2O$ , TBAF (188.7 mg, 0.599 mmol),  $PdCl_2(MeCN)_2$  (5.2 mg, 0.020 mmol),  $P(2-Tol)_3$  (9.1 mg, 0.03 mmol), 1-((4-bromophenoxy)methyl)benzene (105.1 mg, 0.400 mmol) and CuI (39.8 mg, 0.200 mmol) were employed. The crude mixture was analysed by GC-MS [Column: SGE25QC3/BP5 25 m  $\times$  0.25 mm; Carrier gas: He; Oven temp: 60 °C (3 min), 60 °C  $\rightarrow$  300 °C over 12 min]. A yield of 11% for *biphenyl 38r* was deduced from the ratio of peak intensities for 2-(methoxymethyl)naphthalene **8** ( $R_t$  8.1 min,  $m/z$  172) vs. *biphenyl 38r* ( $R_t$  13.3 min,  $m/z$  290).  $m/z$  ( $El^+$ ) (rel. intensity) 290 ( $M^+$ , 20), 91 (100); HRMS ( $El^+$ ) calc'd. for  $C_{20}H_{18}O$  290.1307, found 290.1301,  $\Delta$  -2.0 ppm.

Table 2.6.3, entry 19: **1-(2-Methoxyphenyl)naphthalene 38s**

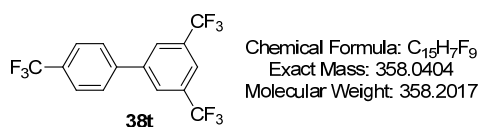


Using *method C*, the crude difluoroarylgermane (44.0 mg, 0.066 mmol) from the photolysis of arylgermane **6e** for 2 h with 8 equivalents of  $Cu(BF_4)_2 \cdot nH_2O$ , TBAF (62.5 mg, 0.198 mmol),  $PdCl_2(MeCN)_2$  (1.7 mg, 0.007 mmol),  $P(2-Tol)_3$  (3.0 mg, 0.0098 mmol), 1-((4-bromophenoxy)methyl)benzene (27.5 mg, 0.133 mmol, 18.5  $\mu$ L) and CuI (13.2 mg, 0.066 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave 1-(2-methoxyphenyl)naphthalene **38s** as a pale yellow oil (4.1 mg, 27 %).

$^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  3.70 (s, 3H,  $\text{OCH}_3$ ), 7.06 (t,  $J = 8.1$  Hz, 1H, ArH), 7.09 (dd,  $J = 7.5, 1.0$  Hz, 1H, ArH), 7.29 (dd,  $J = 7.5, 1.8$  Hz, 1H, ArH), 7.37-7.46 (m, 4H, ArH), 7.53 (d,  $J = 8.1$  Hz, 1H, ArH), 7.58 (d,  $J = 8.5$  Hz, 1H, ArH), 7.87 (t,  $J = 9.1$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  55.6 (q), 110.9 (2d), 120.5 (2d), 125.3 (s), 125.5 (s), 125.6 (2d), 126.4 (d), 127.3 (s), 127.6 (d), 128.1 (d), 129.0 (s), 131.9 (2d), 153.2 (s); HRMS calc'd. for  $\text{C}_{17}\text{H}_{14}\text{O}$  234.1045, found 234.1045 ( $\Delta$  0 ppm).

Table 2.6.3, entry 20: 4-Trifluoromethyl-3',5'-bis-(trifluoromethyl)biphenyl

**38t**<sup>139,140</sup>



Using *method C*, the crude difluoroarylgermane (52.0 mg, 0.074 mmol) from the photolysis of arylgermane **6f** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (70.2 mg, 0.223 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (2.0 mg, 0.0077 mmol),  $\text{P}(2\text{-Tol})_3$  (3.5 mg, 0.0115 mmol), 3,5-bis-trifluoromethylbromobenzene (43.5 mg, 0.149 mmol, 25.6  $\mu\text{L}$ ) and  $\text{CuI}$  (14.8 mg, 0.074 mmol) were employed. The crude mixture was analysed by GC-MS and the yield (26 %) was deduced by the ratio of peak intensity between the 2-(methoxymethyl)naphthalene **8** and the peak for the 2-trifluoromethyl-3',5'-bis-(trifluoromethyl)biphenyl **38t** with  $m/z$  358. HRMS calc'd. for  $\text{C}_{15}\text{H}_7\text{F}_9$  358.0404, found 358.0386 ( $\Delta$  -5.0 ppm).

Table 2.6.3, entry 21: 4-Trifluoromethyl-4'-chloro-1,1'-biphenyl **38u**<sup>240</sup>

Using *method C*, the crude difluoroarylgermane (46.1 mg, 0.066 mmol) from the photolysis of arylgermane **6f** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (62 mg, 0.197 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (1.7 mg, 0.0066 mmol),  $\text{P}(2\text{-Tol})_3$  (3 mg, 0.0099 mmol), 4-chlorobromobenzene (25.1 mg, 0.131 mmol) and  $\text{CuI}$  (13 mg, 0.066 mmol) were employed. The crude mixture was analysed by GC-MS [Column: SGE25QC3/BP5 25 m  $\times$  0.25 mm; Carrier gas: He; Oven temp: 60  $^\circ\text{C}$  (3 min), 60  $^\circ\text{C} \rightarrow$  300  $^\circ\text{C}$  over 12 min]. A yield of 11% for biphenyl **38u** was deduced from the ratio

of peak intensities for *2-(methoxymethyl)naphthalene* **8** ( $R_t$  8.0 min,  $m/z$  172) vs. *biphenyl* **38u** ( $R_t$  10.2 min,  $m/z$  256).  $m/z$  ( $EI^+$ ) (rel. intensity) 256 ( $M^+$ , 50), 141 (100), 115 (45); HRMS ( $EI^+$ ) calc'd. for  $C_{13}H_8^{35}ClF_3$  ( $M^+$ ) 256.0267, found 256.0265,  $\Delta$  -0.6 ppm.

#### ***Cross-coupling of arylgermane 6a with a variety of aryl (pseudo)halides (Table 2.6.4)***

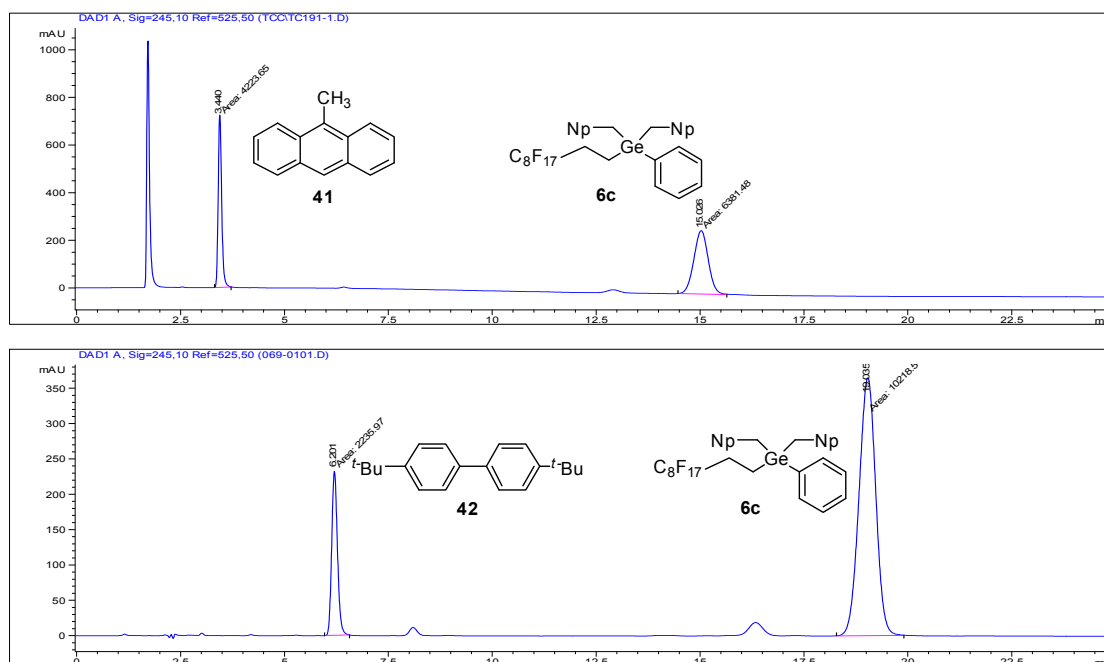
Using *method C*, the crude di-fluoro arylgermane (120.6 mg, 0.1814 mmol) from the photolysis of arylgermane **6a** for 2 h with 8 equivalents of  $Cu(BF_4)_2 \cdot nH_2O$  was charged parallel into three separated vessels (40.2 mg, 0.060 mmol) along with TBAF (56.7 mg, 0.180 mmol),  $PdCl_2(MeCN)_2$  (1.6 mg, 0.006 mmol),  $P(2-Tol)_3$  (2.7 mg, 0.009 mmol) and CuI (12.0 mg, 0.06 mmol). 1-Chloronaphthalene (19.5 mg, 0.12 mmol), 1-iodonaphthalene (30.5 mg, 0.12 mmol) and 1-naphthalenyl triflate (33.1 mg, 0.12 mmol) were employed. The crude mixture was quantified by GC-MS using *2-(methoxymethyl)naphthalene* **8** as an internal standard for evaluation of reaction efficiency. The ratio between *biaryl* **38d** and *2-(methoxymethyl)naphthalene* **8** obtained by bromonaphthalene was deemed as 100 % in comparison with the outcomes furnished by the other analogues.

#### ***Stability profiling of fluororous-tagged phenylgermane 6c (Table 2.6.5)***

Stability tests were carried out using 8 different conditions on fluororous-tagged arylgermane **6c** as substrate with 9-methylanthracene **41** and 4,4'-di-*tert*-butyl-1,1'-biphenyl **42** as internal standard.<sup>146</sup> To a solution of fluororous-tagged arylgermane **6c** (5 mg), internal standard **41** or **42** (1 mg) in reaction solvents (5 mL) at RT for 3 h. The reaction mixtures were quenching with water (5 mL) and diluted with  $Et_2O$  (5 mL) followed by extracted with  $Et_2O$  (10 mL  $\times$  5). The organic layer was dried by  $N_2$  flow. The residue was dissolved with acetonitrile (5 mL) and analysed by HPLC. *HPLC conditions:*

Agilent 1100 HPLC; Column: XTerra RP8 4.6 mm × 150mm, 5μ; Mobile phase: MeCN/H<sub>2</sub>O = 80:20; Flow rate: 1 mL/min; Detection: UV diode array at 245 nm; Injection volume: 2μL

The ratio of the peak areas was calculated for substrate **6c** and internal standard **41** or **42**. In The percentage recovery of compound **6c** was compared to blank tests in appropriate solvents using in these different conditions. The chromatographs of the blank tests were shown as below (Figure 4.1).



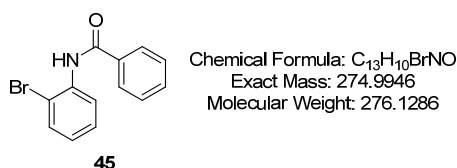
| No. | Conditions <sup>a</sup>                         | Ref. | Rec. 6c/% (Run 1) <sup>a</sup> | Rec. 6c/% (Run 2) <sup>a</sup> | Rec.6c/% (Mean) <sup>a</sup> |
|-----|-------------------------------------------------|------|--------------------------------|--------------------------------|------------------------------|
| 1   | HS(CH <sub>2</sub> ) <sub>2</sub> OH, DBU, DMF  | 41   | 109                            | 95                             | 102                          |
| 2   | Piperidine/DMF (20% v/v)                        | 41   | 111                            | 91                             | 101                          |
| 3   | Hydrazine/DMF (2% v/v)                          | 41   | 114                            | 93                             | 104                          |
| 4   | NaBH <sub>4</sub> , THF                         | 41   | 106                            | 107                            | 107                          |
| 5   | LiAlH <sub>4</sub> , THF                        | 41   | 97                             | 110                            | 104                          |
| 6   | TBAF, THF                                       | 41   | 101                            | 103                            | 102                          |
| 7   | TFA/CH <sub>2</sub> Cl <sub>2</sub> (50% v/v)   | 41   | 18                             | 22                             | 20                           |
| 8   | <i>m</i> -CPBA, CH <sub>2</sub> Cl <sub>2</sub> | 42   | 75                             | 76                             | 76                           |

<sup>a</sup>% recovery of **6c** by HPLC vs. the internal standards.

**Figure 4.1.** Showing stability profile of fluorous-tagged phenylgermane **6c**

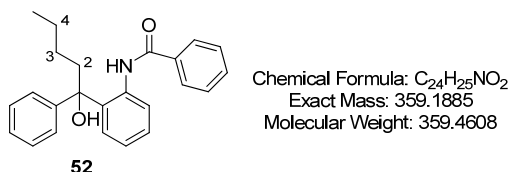
## Synthesis of boscalid and analogues by germyl-Stille cross-coupling

### *N*-Benzoyl-2-bromoaniline **45**<sup>241</sup>



To a solution of 2-bromoaniline (0.20 g, 1.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL), DMAP (0.0142 g, 0.116 mmol) and Et<sub>3</sub>N (0.35 g, 3.48 mmol, 0.49 mL) was added benzoyl chloride (0.18 g, 1.28 mmol, 0.15 mL) under 0 °C. The resulting reaction mixture was stirred at 0 °C for 3 h. The yellow reaction was quenching dropwise with water until effervescence ceased. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (2 × 20.0 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo* followed by purification by FC (hexane/EtOAc 80/20) and drying under high vacuum gave *N*-benzoyl-2-bromoaniline **45** as white needles (0.296 g, 92 %). mp 106-108 °C; <sup>1</sup>H NMR (270 MHz; CDCl<sub>3</sub>): δ 7.09-7.25 (m, 2H, ArH), 7.31-7.38 (m, 2H, ArH), 7.39-7.49 (m, 2H, ArH), 7.58-7.68 (m, 1H, ArH), 7.81 (dd, *J* = 7.1, 1.7 Hz, 2H, ArH), 8.12 (dd, *J* = 7.2, 1.3 Hz, 1H, ArH).

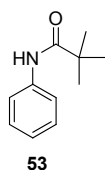
### *N*-(2-(1-Hydroxy-1-phenylpentyl)phenyl)benzamide **52**



To a solution of *N*-benzoyl-2-bromoaniline **45** (0.10 g, 0.362 mmol) in THF (10.0 mL) at -100 °C was added a solution of <sup>n</sup>BuLi (0.32 mL, 0.724 mmol, 2.5 M in hexanes) dropwise resulting in a yellow solution. The solution was stirred at -100 °C for 30 min before addition of trimethylstannyl chloride (0.22 g, 1.09 mmol) at -100 °C and stirred for 1 h then warmed up to RT for 16 h. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred. Following extraction with (2 × 20.0 mL) of Et<sub>2</sub>O, the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give a white residue which was purified by FC (hexane/EtOAc, 90/10) to give the

*N*-(2-(1-hydroxy-1-phenylpentyl)phenyl)benzamide **52** as white needles (0.053 g, 41 %). mp 156-158 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 0.89 (t, *J* = 7.3 Hz, 3H, CH<sub>3</sub>), 1.19 (m, 1H, H-3), 1.34 (m, 2H, H-4), 1.49 (m, 1H, H-3), 2.24 (tdd, *J* = 11.8, 4.7, 1.8 Hz, 1H, H-2), 2.32 (tdd, *J* = 11.8, 4.7, 1.8 Hz, 1H, H-2), 3.09 (s, 1H, OH), 7.11-7.20 (m, 4H, ArH), 7.25-7.28 (m, 2H, ArH), 7.34-7.41 (m, 3H, ArH), 7.44-7.51 (m, 2H, ArH), 7.63 (dd, *J* = 7.2, 1.1 Hz, 2H, ArH), 8.39 (d, *J* = 7.6 Hz, 1H, ArH), 9.93 (s, 1H, NH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 14.0 (q), 23.0 (t), 25.8 (t), 42.7 (t), 79.5 (s), 123.2 (d), 123.3 (d), 125.5 (2d), 126.7 (d), 127.0 (2d), 127.1 (d), 128.1 (2d), 128.3 (2d), 128.6 (d), 131.4 (d), 134.5 (s), 135.0 (s), 137.7 (s), 144.7 (s), 165.0 (s); IR ν<sub>max</sub> (neat) 3294 (brs, OH), 3050 (C-H), 2940 (C-H), 1656 (C=O), 1584 (C=C), 1527, 1449, 751, 700 cm<sup>-1</sup>; *m/z* (CI<sup>+</sup>) (rel. intensity) 360 (M<sup>+</sup>, 15), 302 (25), 236 (35), 105 (100), 77 (40); HRMS (CI<sup>+</sup>) calc'd. for C<sub>24</sub>H<sub>25</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 360.1964, found 360.1961 (Δ 0.7 ppm).

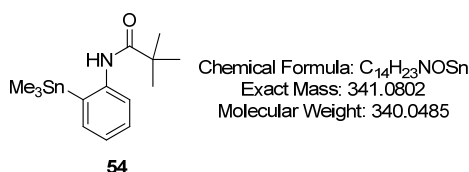
### *N*-Pivaloylanilide **53**<sup>146</sup>



Chemical Formula: C<sub>11</sub>H<sub>15</sub>NO  
Exact Mass: 177.1154  
Molecular Weight: 177.2429

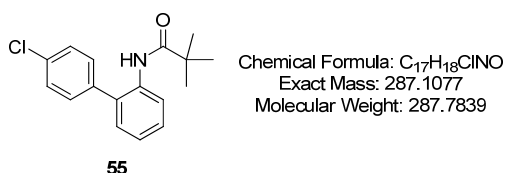
To a solution of aniline (0.20 g, 2.15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL) was added pivaloyl chloride (0.39 g, 3.22 mmol, 0.40 mL) and NaOH (10 mL, 25 %) under 0 °C. The resulting reaction mixture was stirred at 0 °C for 4 h. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (2 × 20.0 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo*. Purification by FC (hexane/EtOAc 85/15) and drying under high vacuum gave *N*-pivaloylanilide **53** as white needles (0.37 g, 97 %); <sup>1</sup>H NMR (270 MHz; CDCl<sub>3</sub>): δ 1.30 (s, 9H, 3 × CH<sub>3</sub>), 7.08 (tt, *J* = 7.6, 1.3 Hz, 1H, ArH), 7.30 (t, *J* = 7.6 Hz, 2H, ArH), 7.51 (d, *J* = 7.6 Hz, 2H, ArH).

## 2-Trimethylstannyl-*N*-pivaloylanilide **54**<sup>146,147</sup>



To a solution of *N*-pivaloylanilide **53** (0.10 g, 0.564 mmol) and TMEDA (0.066 g, 0.564 mmol, mL) in THF (10.0 mL) at -20 °C was added a solution of <sup>*n*</sup>BuLi (0.5 mL, 1.25 mmol, 2.5 M in hexanes) dropwise resulting in a yellow solution. The solution was stirred at -20 °C for 30 min before addition of trimethylstannyl chloride (0.34 g, 1.71 mmol) at -20 °C, stirring for 1 h and then warming to RT for 16 h. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred. Following extraction with (2 × 20.0 mL) of Et<sub>2</sub>O, the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give white residue which was purified by FC (hexane/EtOAc, 90/10) to give 2-trimethylstannyl-*N*-pivaloylanilide **54** as white needles (0.064 g, 67 %) with recovery of *N*-pivaloylanilide **53** (0.05g, 50 %); <sup>1</sup>H NMR (270 MHz; CDCl<sub>3</sub>): δ 0.49 (s, 9H, 3 × SnCH<sub>3</sub>), 1.29 (s, 9H, 3 × CH<sub>3</sub>), 7.07 (t, *J* = 7.7 Hz, 1H, ArH), 7.29 (t, *J* = 7.7 Hz, 2H, ArH), 7.37 (brs, 1H, NH), 7.50 (d, *J* = 7.7 Hz, 1H, ArH).

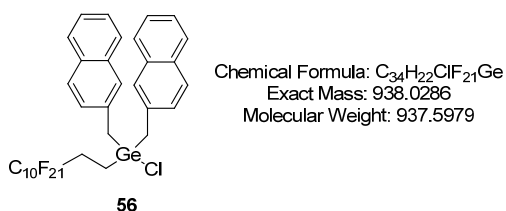
## 4-Chloro-2'-*N*-pivaloylanilinylbiphenyl **55**



To a solution of 2-trimethylstannyl-*N*-pivaloylanilide **54** (0.05 g, 0.147 mmol), CsF (0.447 g, 0.294 mmol, mL), CuI (0.001 g, 0.005 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.004 g, 0.003 mmol) in DMF (10.0 mL) was added 4-chloro-bromobenzene (0.014 g, 0.073 mmol) at rt. The solution was evacuated/ purged with N<sub>2</sub> for five times and heated to 40 °C for 16 h.<sup>155</sup> The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred. Following extraction with (2 × 20.0 mL) of Et<sub>2</sub>O, the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give a white residue which was purified by FC (hexane/EtOAc, 90/10) to give 4-chloro-2'-*N*-pivaloylanilinylbiphenyl **55** as white needles (0.012 g, 58 %); <sup>1</sup>H

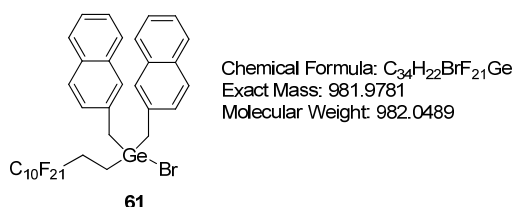
NMR (270 MHz; CDCl<sub>3</sub>):  $\delta$  1.08 (s, 9H, 3  $\times$  CH<sub>3</sub>), 7.14 (d,  $J$  = 7.7 Hz, 2H, ArH), 7.24-7.39 (m, 3H, ArH), 7.45 (d,  $J$  = 8.2 Hz, 2H, ArH), 8.29 (d,  $J$  = 8.2 Hz, 1H, ArH); HRMS (EI) calc. for C<sub>17</sub>H<sub>18</sub>ClNO 287.1077, found 287.1077 ( $\Delta$  0 ppm).

**Chloro-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heneicosafuorododecyl)bis(naphthalen-2-ylmethyl)germane 56**



To a solution of (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heneicosafuorododecyl)-(4-methoxyphenyl)bis(naphthalen-2-ylmethyl)germane (0.50 g, 0.495 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL) was added a solution of conc. HCl (10 mL, 37 % wt.). The resulting biphasic reaction mixture was stirred at rt for 12 h, extracted with Et<sub>2</sub>O (3  $\times$  20.0 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give *chlorogermane* **56** as a brown amorphous solid (0.455 g, 98 %). mp 175-177 °C; <sup>1</sup>H NMR (270 MHz; CDCl<sub>3</sub>):  $\delta$  1.25 (m, 2H, C<sub>10</sub>F<sub>21</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 1.83 (m, 2H, C<sub>10</sub>F<sub>21</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 2.88 (d,  $J$  = 12.6 Hz, 2H, GeCH<sub>2</sub>NP), 2.90 (d,  $J$  = 12.6 Hz, 2H, GeCH<sub>2</sub>NP), 7.21 (m, 2H, ArH), 7.42-7.49 (m, 6H, ArH), 7.68 (m, 2H, ArH), 7.76 (m, 2H, ArH), 7.81 (m, 2H, ArH).

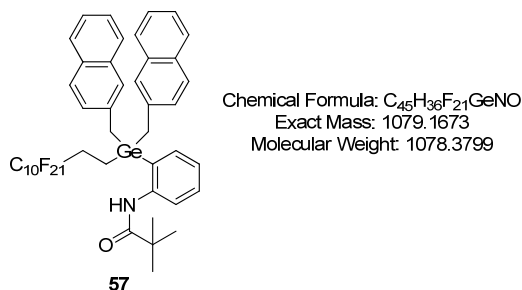
**Bromo-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heneicosafuorododecyl)bis(naphthalen-2-ylmethyl)germane 61**



According the method of Noban,<sup>156</sup> to a solution of (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heneicosafuorododecyl)-(4-methoxyphenyl)bis(naphthalen-2-ylmethyl)germane (0.120 g, 0.119 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added a solution of conc. HBr (2.0 mL, 48% wt.). The

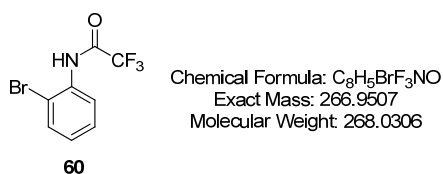
resulting biphasic reaction mixture was stirred at rt for 12 h, extracted with Et<sub>2</sub>O (3 × 20.0 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give *bromogermane 61* as a brown amorphous solid (0.087 g, 88%); <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 1.39 (m, 2H, C<sub>10</sub>F<sub>21</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 1.93 (m, 2H, C<sub>10</sub>F<sub>21</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 2.97 (d, *J* = 12.6 Hz, 2H, GeCH<sub>2</sub>NP), 3.00 (d, *J* = 12.6 Hz, 2H, GeCH<sub>2</sub>NP), 7.21 (dd, *J* = 6.6, 1.8 Hz, 2H, ArH), 7.42-7.49 (m, 6H, ArH), 7.68 (dd, *J* = 6.6, 1.8 Hz, 2H, ArH), 7.76 (d, *J* = 8.4 Hz, 2H, ArH), 7.81 (dd, *J* = 6.6, 1.8 Hz, 2H, ArH).

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heneicosafuorododecyl)  
-(2-*N*-pivaloylacetanilidyl)bis(naphthalen-2-ylmethyl)germane 57**



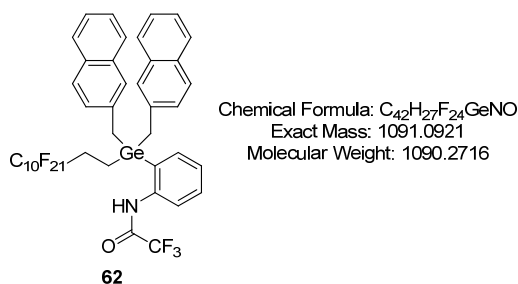
To a solution of *N*-pivaloylanilide **53** (0.05 g, 0.282 mmol) in Et<sub>2</sub>O (10.0 mL) at -20 °C was added a solution of <sup>*n*</sup>BuLi (0.283 mL, 0.706 mmol, 2.5M in hexanes) dropwise resulting in a yellow solution. The solution was stirred at -20 °C for 30 min before addition of chlorogermane **56** (0.05 g, 0.053 mmol) at -20 °C, stirring for 1 h and then warming to RT for 16 h. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred. Following extraction with (2 × 20.0 mL) of Et<sub>2</sub>O, the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give green oily residue which was purified by FC (hexane/EtOAc, 90/10) to give 2-(*N*-pivaloylacetanilidyl)germane **57** contaminated with an inseparable by-product as a pale yellow oil (0.036 g); <sup>1</sup>H NMR (270 MHz; CDCl<sub>3</sub>): δ 0.79-0.84 (m, 11H, 3 × CH<sub>3</sub> + by-product), 1.24-1.31 (m, 8H, CH<sub>2</sub>CH<sub>2</sub>Ge + by-product), 1.78 (m, 2H, C<sub>10</sub>F<sub>21</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 2.74 (s, 4H, 2 × GeCH<sub>2</sub>NP), 7.11 (dd, *J* = 8.4, 1.8 Hz, 2H, ArH), 7.31-7.41 (m, 10H, ArH), 7.64 (d, *J* = 7.6 Hz, 2H, ArH), 7.70 (d, *J* = 8.4 Hz, 2H, ArH), 7.68 (d, *J* = 8.4 Hz, 2H, ArH), 7.76 (d, *J* = 7.2 Hz, 2H, ArH).

## 2-Bromo-trifluoroacetanilide **60**<sup>155</sup>



To a solution of 2-bromoaniline (0.50 g, 2.91 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL), DMAP (0.035 g, 0.291 mmol) and Et<sub>3</sub>N (1.38 g, 13.7 mmol, 1.9 mL) was added trifluoroacetic anhydride (1.35 g, 6.44 mmol, 0.91 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenching dropwise with water until effervescence ceased. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (2 × 20.0 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo* followed by purification by FC (hexane/EtOAc 80/20) and drying under high vacuum gave *2-bromo-trifluoroacetanilide* **60** as white needles (0.73 g, 95 %). mp 60-61 °C; <sup>1</sup>H NMR (270 MHz; CDCl<sub>3</sub>): δ 7.11 (td, *J* = 7.7, 1.4 Hz, 1H, ArH), 7.38 (td, *J* = 8.2, 1.4 Hz, 1H, ArH), 7.60 (td, *J* = 8.2, 1.4 Hz, 1H, ArH), 8.30 (dd, *J* = 8.2, 1.4 Hz, 1H, ArH), 8.45 (brs, 1H, NH).

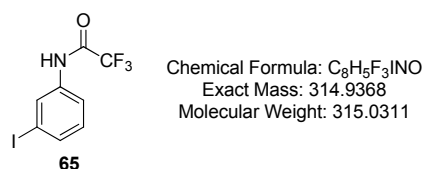
## (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heneicosafuorododecyl)-(2-trifluoroacetanilidyl)bis(naphthalen-2-ylmethyl)germane **62**



To a solution of 2-bromotrifluoroacetanilide **60** (0.029 g, 0.109 mmol) in THF (10.0 mL) at -78 °C was added a solution of MeLi (71 μL, 0.114 mmol, 1.6 M in diethyl ether) for 30 min to deprotonation of amide. A solution of a solution of <sup>t</sup>BuLi (338 μL, 0.491 mmol, 1.45M in pentane) was added dropwise resulting in a yellow solution. The solution was stirred at -78 °C for 30 min before addition of bromogermane **61** (0.051 g, 0.054 mmol) at -78 °C and stirred for 1 h than warmed up to RT for 16 h. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and a

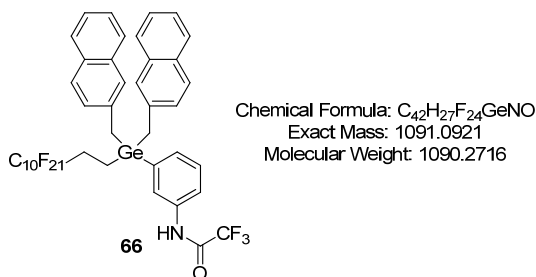
solution of 1.0 M  $\text{NH}_4\text{Cl}$  was added to the reaction mixture until no effervescence occurred. Following extraction with ( $2 \times 20.0$  mL) of  $\text{Et}_2\text{O}$ , the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to give a yellow oily residue which was purified by FC (hexane/ $\text{EtOAc}$ , 90/10) to give 2-(*N*-trifluorotrifluoroacetanilidyl)germane **62** contaminated with an inseparable by-product as a pale yellow oil (0.036 g);  $^1\text{H}$  NMR (270 MHz;  $\text{CDCl}_3$ ):  $\delta$  0.82-0.85 (m, 4H, by-product), 1.15-1.29 (m, 12H,  $\text{CH}_2\text{CH}_2\text{Ge}$  + by-product), 1.78 (m, 2H,  $\text{C}_{10}\text{F}_{21}\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.76 (s, 4H,  $2 \times \text{GeCH}_2\text{NP}$ ), 7.06 (dd,  $J = 8.9, 1.0$  Hz, 2H, ArH), 7.35-7.49 (m, 10H, ArH), 7.61 (d,  $J = 6.7$  Hz, 2H, ArH), 7.70 (d,  $J = 8.4$  Hz, 2H, ArH), 7.71 (d,  $J = 8.5$  Hz, 2H, ArH), 7.77 (d,  $J = 7.4$  Hz, 2H, ArH).

### 3-Iodo-trifluoroacetanilide **65**<sup>242</sup>



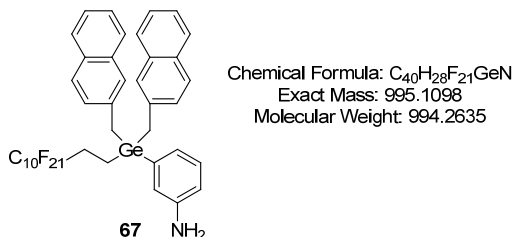
To a solution of 3-iodoaniline (0.42 g, 1.92 mmol) in  $\text{CH}_2\text{Cl}_2$  (10.0 mL) and  $\text{Et}_3\text{N}$  (0.47 g, 4.69 mmol, 0.65 mL) was added trifluoroacetic anhydride (0.803 g, 3.82 mmol, 0.54 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenching dropwise with water and diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and washed with water ( $2 \times 20.0$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and the solvent was removed *in vacuo* followed by purification by FC (hexane/ $\text{EtOAc}$  80/20) and drying under high vacuum gave 3-iodo-trifluoroacetanilide **65** as white plates (0.602 g, 98 %). mp 74-75 °C;  $^1\text{H}$  NMR (270 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.11 (d,  $J = 8.1$  Hz, 1H, ArH), 7.55 (t,  $J = 7.8$  Hz, 2H, ArH), 7.85 (brs, 1H, NH), 7.95 (s, 1H, ArH).

**3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heneicosafuorododecyl)  
-(3-*N*-trifluorotrifluoroacetanilidyl)bis(naphthalen-2-ylmethyl)germane 66**



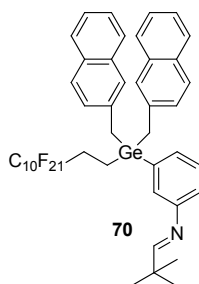
To a solution of 3-iodotrifluoroacetanilide **65** (0.055 g, 0.175 mmol) in THF (10.0 mL) at 0 °C was added NaH (0.007 g, 0.175 mmol, 60 % in mineral oil). After stirring at 0 °C for 30 min, the solution was cooled to -78 °C and a solution of <sup>t</sup>BuLi (315 μL, 0.437 mmol, 1.4M in pentane) was added dropwise resulting in a yellow solution. The solution was stirred at -78 °C for 30 min before addition of bromogermane **61** (0.050 g, 0.054 mmol) at -78 °C, stirring for 1 h and then warming to RT for 16 h. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred. Following extraction with (2 × 20.0 mL) of Et<sub>2</sub>O, the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give yellow oily residue which was purified by FC (hexane/EtOAc, 90/10) to give 3-(*N*-trifluorotrifluoroacetanilidyl)germane **66** as a pale yellow oil (0.0254 g, 46 %); <sup>1</sup>H NMR (270 MHz; CDCl<sub>3</sub>): δ 0.82-0.85 (m, 4H, by-product ), 1.15-1.29 (m, 12H, CH<sub>2</sub>CH<sub>2</sub>Ge + by-product ), 1.78 (m, 2H, C<sub>10</sub>F<sub>21</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 2.76 (s, 4H, 2 × GeCH<sub>2</sub>NP), 7.11 (d, *J* = 8.1 Hz, 1H, ArH), 7.32-7.52 (m, 10H, ArH), 7.60 (d, *J* = 6.7 Hz, 2H, ArH), 7.72 (d, *J* = 8.4 Hz, 2H, ArH), 7.74 (d, *J* = 8.5 Hz, 2H, ArH), 7.77 (d, *J* = 7.4 Hz, 1H, ArH).

**3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heneicosafuorododecyl)-(3-aminophenyl)bis(naphthalen-2-ylmethyl)germane **67****



To a solution of 3-(*N*-trifluoroacetanilidyl)germane **66** (0.025 g, 0.023 mmol) and TBAI (0.001 g, 0.003 mmol) in THF (5.0 mL) was added NaOH<sub>(aq)</sub> (40 %, 5.0 mL). The solution was heated to 60 °C for 48 h. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture. Following extraction with Et<sub>2</sub>O (2 × 20.0 mL), the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give yellow oily residue which was purified by FC (hexane/EtOAc, 85/15) to give (3-aminophenyl)germane **67** as a pale yellow oil (0.0123 g, 54 %); <sup>1</sup>H NMR (270 MHz; CDCl<sub>3</sub>): δ 1.16 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 1.78 (m, 2H, C<sub>10</sub>F<sub>21</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 2.74 (s, 4H, 2 × GeCH<sub>2</sub>NP), 3.82 (brs, 2H, NH<sub>2</sub>), 7.08 (d, *J* = 8.1 Hz, 1H, ArH), 7.29-7.45 (m, 10H, ArH), 7.56 (d, *J* = 6.7 Hz, 2H, ArH), 7.70 (d, *J* = 8.4 Hz, 2H, ArH), 7.72 (d, *J* = 8.5 Hz, 2H, ArH), 7.74 (d, *J* = 7.4 Hz, 1H, ArH).

**3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heneicosafuorododecyl)-(3-*N*-pivalylimineyl)bis(naphthalen-2-ylmethyl)germane **70****

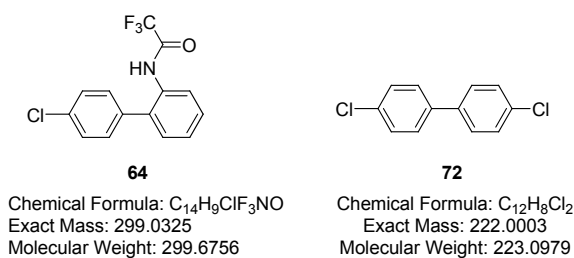


To a solution of (3-aniliny)germane **67** (0.0123 g, 0.124 mmol) and 4-TsOH (0.001 g, 0.006 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) in the presence of 3 Å MS (10 mg) was added pivalaldehyde (0.011 g, 0.129 mmol, 14 μL). The solution was stirred at rt for 48 h. The reaction was monitored by TLC. After the starting material had been consumed, the mixture was diluted with Et<sub>2</sub>O (20.0 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was

added to the reaction mixture. Following extraction with Et<sub>2</sub>O (2 × 20.0 mL), the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give a pale yellow oil which was subjected into photolysis/cross-coupling reaction without further purification.

***N*-(4'-Chlorobiphenyl-2-yl)-2,2,2-trifluoroacetamide **64** and**

**4,4'-Dichloro-1,1'-biphenyl **72****<sup>243</sup>

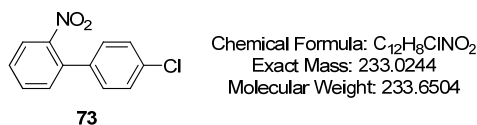


Using *method C*, the crude difluoroarylgermane from the photolysis of arylgermane **6d** (35.7 mg, 0.053 mmol) for 1 h with 4 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (50.4 mg, 0.16 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (1.4 mg, 0.005 mmol), P(2-Tol)<sub>3</sub> (2.5 mg, 0.081 mmol), 2-bromo-trifluoroacetanilide **60** (28.6 mg, 0.17 mmol) and CuI (10.2 mg, 0.051 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave:

*N*-(4'-Chlorobiphenyl-2-yl)-2,2,2-trifluoroacetamide **64** as a pale yellow oil (5.6 mg, 35 %); <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 6.77 (dd, *J* = 7.9, 1.0 Hz, 1H, ArH), 6.83 (td, *J* = 7.6, 1.0 Hz, 1H, ArH), 7.09 (dd, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.17 (td, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.38-7.46 (m, 3H, ArH), 7.48 (brs, 1H, NH), 8.27 (d, *J* = 8.2 Hz, 1H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 115.7 (d), 118.7 (d), 119.2 (s), 126.3 (s), 128.8 (d), 129.0 (2d), 130.3 (d), 130.5 (2d), 133.1 (s), 137.9 (s), 143.4 (s), 160.2 (s); IR ν<sub>max</sub> (neat) 3345 (N-H), 3084 (C-H), 2935 (C-H), 1745 (C=O), 1585 (C=C), 1068, 810 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) (rel. intensity) 301 [(M<sup>37</sup>Cl)<sup>+</sup>, 25], 299 [(M<sup>35</sup>Cl)<sup>+</sup>, 76], 230 (20), 167 (55), 149 (50), 55 (100); HRMS calc'd. For C<sub>14</sub>H<sub>9</sub>ClF<sub>3</sub>NO 299.0325, found 299.0322 (Δ -1.0 ppm).

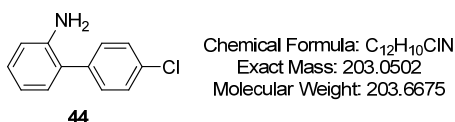
4,4'-dichloro-1,1'-biphenyl **72** as a colourless oil (6.3 mg, 53 %); <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 7.45 (d, *J* = 8.2 Hz, 4H), 7.37 (d, *J* = 8.2 Hz, 4H); HRMS calc'd. For C<sub>12</sub>H<sub>8</sub>Cl<sub>2</sub> 222.0003, found 221.9998 (Δ -2.1 ppm).

#### 4-Chloro-2'-nitrobiphenyl **73**



Using *method C*, the crude difluoroarylgermane (37.7 mg, 0.056 mmol) from the photolysis of arylgermane **6d**, TBAF (53.3 mg, 0.169 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (1.5 mg, 0.006 mmol), P(2-Tol)<sub>3</sub> (2.6 mg, 0.0087 mmol), 2-bromo-nitrobenzene (22.8 mg, 0.113 mmol) and CuI (11.2 mg, 0.056 mmol) were employed. Purification by FC (hexane/EtOAc, 94/6) gave *4-chloro-2'-nitrobiphenyl* **73** as a colourless oil (8.1 mg, 61 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 7.27 (d, *J* = 7.0 Hz, 2H, ArH), 7.40-7.44 (m, 3H, ArH), 7.53 (td, *J* = 7.8, 1.3 Hz, 1H, ArH), 7.65 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.90 (dd, *J* = 8.2, 1.0 Hz, 1H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 124.3 (d), 128.5 (d), 128.9 (2d), 129.3 (2d), 131.8 (d), 132.5 (d), 134.5 (s), 135.2 (s), 135.9 (s), 149.0 (s); IR ν<sub>max</sub> (neat) 3054, 2986, 1588, 1535, 1472, 1265, 1009, 818, 738 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) (rel. intensity) 235 [(M<sup>37</sup>Cl)<sup>+</sup>, 15], 233 [(M<sup>35</sup>Cl)<sup>+</sup>, 45], 199 (70), 156 (80), 141 (100); HRMS calc'd. for C<sub>12</sub>H<sub>8</sub>ClNO<sub>2</sub> 233.0244, found 233.0241 (Δ -1.1 ppm).

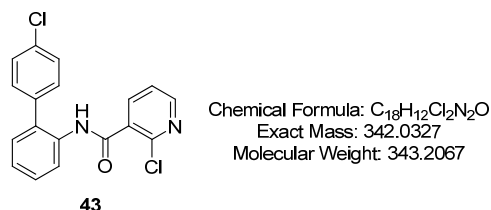
#### 4-Chloro-2'-ylaminebiphenyl **44**<sup>244</sup>



To a solution of 4-chloro-2'-nitrobiphenyl **73** (15 mg, 0.064 mmol) in THF-EtOH (1:1, 10 mL) was added tin(II) chloride (122 mg, 0.64 mmol) and conc. HC (1 mL), the reaction mixture was stirred for 16 h. A sat. solution of K<sub>2</sub>CO<sub>3</sub> was added to the reaction mixture and the reaction mixture was partitioned between Et<sub>2</sub>O (40.0 mL) and water (10.0 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10.0 mL) and dried over MgSO<sub>4</sub>. Purification by FC (hexane/EtOAc, 90/10) gave *4-chloro-2'-ylaminebiphenyl* **44** as a colourless oil (10.3 mg, 88 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 3.73 (brs, 2H, NH<sub>2</sub>), 6.77 (dd, *J* = 7.9, 1.0 Hz, 1H, ArH), 6.83 (td, *J* = 7.6, 1.0 Hz, 1H, ArH), 7.09 (dd, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.17 (td, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.38-7.46 (m, 4H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 115.7 (d), 118.7 (d), 126.3 (s), 128.8 (d), 129.0

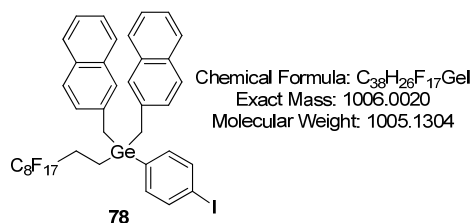
(2d), 130.3 (d), 130.5 (2d), 133.1 (s), 137.9 (s), 143.4 (s); IR  $\nu_{\max}$  (neat) 3475, 3383, 3083, 1886, 1616, 1472, 1087, 1008, 810, 744  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 205  $[(\text{M}^{37}\text{Cl})^+, 9]$ , 203  $[(\text{M}^{35}\text{Cl})^+, 25]$ , 167 (25), 49 (30), 84 (90), 49 (100); HRMS calc'd. for  $\text{C}_{12}\text{H}_{10}\text{ClN}$  203.0502, found 203.0501 ( $\Delta$  -0.4 ppm).

### Boscalid (**43**)<sup>162</sup>



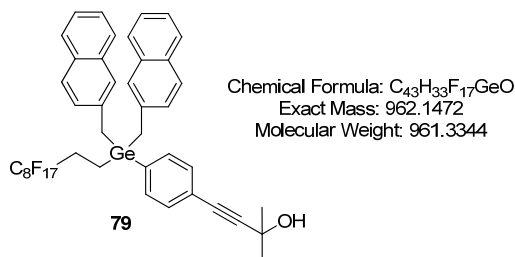
To a solution of 4-chloro-2'-ylaminebiphenyl **44** (20.0 mg, 0.098 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added 2-chloro-3-nicotinic acid (17.3 mg, 0.098 mmol), DMAP (0.5 mg, 0.004 mmol) and DCC (22.3 mg, 0.108 mmol), the reaction mixture was stirred for 16 h. A sat. solution of  $\text{K}_2\text{CO}_3$  was added to the reaction mixture and the reaction mixture was partitioned between  $\text{Et}_2\text{O}$  (40.0 mL) and water (10.0 mL), extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10.0$  mL) and dried over  $\text{MgSO}_4$ . Purification by FC (hexane/ $\text{EtOAc}$ , 75/25) gave *boscalid* **43** as a colourless oil (22.1 mg, 65 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.27 (d,  $J = 4.8$  Hz, 2H, ArH), 7.31-7.36 (m, 3H, ArH), 7.41-7.47 (m, 3H, ArH), 8.13 (dd,  $J = 7.7, 1.2$  Hz, 1H, ArH), 8.16 (brs, 1H, NH), 8.41 (d,  $J = 8.2$  Hz, 1H, ArH), 8.44 (dd,  $J = 4.6, 1.7$  Hz, 1H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  122.1 (d), 122.9 (d), 125.3 (d), 128.9 (d), 129.3 (2d), 130.2 (d), 130.8 (2d), 131.0 (s), 132.2 (s), 134.3 (s), 134.4 (s), 136.2 (s), 140.1 (d), 146.6 (s), 151.3 (d), 162.5 (s); IR  $\nu_{\max}$  (neat) 3338 (N-H), 3084 (C-H), 2935 (C-H), 1887 (comb), 1656 (C=O), 1580 (C=C), 1472, 810  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 347  $[(\text{M}^{37,37}\text{Cl}) + \text{H}^+, 10]$ , 345  $[(\text{M}^{37,35}\text{Cl}) + \text{H}^+, 35]$ , 343  $[(\text{M}^{35,35}\text{Cl}) + \text{H}^+, 40]$ , 309 (15), 225 (100); HRMS ( $\text{CI}^+$ ) calc'd. for  $\text{C}_{18}\text{H}_{13}\text{Cl}_2\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$  343.0405, found 343.0409 ( $\Delta$  1.1 ppm).

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl)(4-iodophenyl)germane 78**



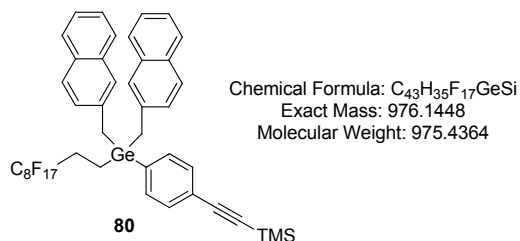
To a solution of 1,4-diiodobenzene (0.1258 g, 0.382 mmol) in THF (10.0 mL) at  $-78^{\circ}\text{C}$  was added a solution of  $t\text{BuLi}$  (0.546 mL, 0.764 mmol, 1.4M in pentane) dropwise resulting in a dark red solution. The solution was stirred at  $-78^{\circ}\text{C}$  for 30 min before addition of bromogermane **40** (0.281 g, 0.319 mmol) at  $-78^{\circ}\text{C}$ , stirring for 1 h and then warming to RT for 16 h. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and a solution of 1.0 M  $\text{NH}_4\text{Cl}$  was added to the reaction mixture until no effervescence occurred. Following extraction with ( $2 \times 20.0$  mL) of  $\text{Et}_2\text{O}$ , the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to give yellow oily residue which was purified by FC (hexane/ $\text{EtOAc}$ , 97/3) to give pure *l*-(4-iodophenyl)germane **78** as a pale yellow oil (0.4706 g, 87 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.20 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 1.87 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.77 (s, 4H,  $2 \times \text{GeCH}_2\text{NP}$ ), 7.07 (dd,  $J = 6.7, 1.7$  Hz, 2H, ArH), 7.25 (d,  $J = 8.2$  Hz, 2H, ArH), 7.35 (d,  $J = 7.7$  Hz, 2H, ArH), 7.41-7.47 (m, 6H, ArH), 7.65 (d,  $J = 7.7$  Hz, 2H, ArH), 7.70 (d,  $J = 8.2$  Hz, 2H, ArH), 7.79 (d,  $J = 7.7$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  1.8 (t), 22.4 (2t), 26.2 (t,  $J_{\text{CF}} = 23.0$  Hz), 96.2 (s), 108.3 (s), 110.2 (s), 110.7 (3s), 110.97 (s), 111.01 (s), 117.9 (s), 125.0 (2d), 125.7 (2d), 126.2 (2d), 127.0 (2d), 127.2 (2d), 127.6 (2d), 128.2 (2d), 128.6 (2d), 131.3 (2s), 133.7 (2s), 135.1 (2d), 135.7 (s), 136.1 (2s);  $^{19}\text{F}$  NMR (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -126.1 (s, 2F), -123.6 (s, 2F), -122.7 (s, 2F), -121.9 (m, 6F), -116.3 [quintet,  $J = 14.5$  Hz, 2F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ], -80.7 [t,  $J = 10$  Hz, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ]; IR  $\nu_{\text{max}}$  (neat) 3035 (C-H), 2988 (C-H) 1549 (C=C), 1421 (C-F), 1265, 1050 (C-I), 896, 740  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{FAB}^+$ ) (rel. intensity) 864  $[(\text{M}-\text{NpCH}_2)^+, 2]$ , 803 (1), 709 (5), 141 (100); HRMS ( $\text{FAB}^+$ ) calc'd. for  $\text{C}_{27}\text{H}_{17}\text{F}_{17}^{74}\text{GeI} [(\text{M}-\text{NapCH}_2)^+]$  864.9310, found 864.9307 ( $\Delta$  -0.3 ppm).

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl){4-[(3-methyl-3-hydroxybutynyl)phenyl]}germane **79****



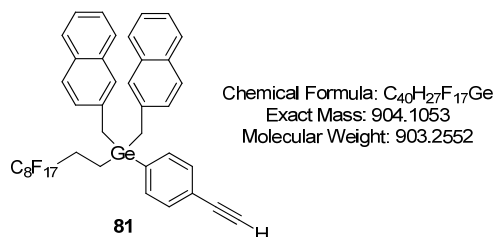
According to the method of Menchi's conditions, <sup>163</sup>Pd(OAc)<sub>2</sub> (1.5 mg, 0.007 mmol) and PPh<sub>3</sub> (5.5 mg, 0.128 mmol) were dissolved in DMF (1.0 mL) for 30 min to give a solution of the active Pd(0) catalyst. The catalyst solution was added to the (4-iodophenyl)germane **78** (128.5 mg, 0.128 mmol) solution followed by adding 2-methylbut-3-yn-2-ol (21.5 mg, 0.256 mmol, 25  $\mu$ L), CuI (2.8 mg, 0.014 mmol) and <sup>n</sup>BuNH<sub>2</sub> (5 mL). The solution mixture was warmed to 55 °C for 16 h under nitrogen atmosphere. The resulting solution was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (3  $\times$  10.0 mL), the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo*. Purification by FC (hexane/EtOAc, 85/15) gave *germane 79* as a pale yellow oil (83.6 mg, 68 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  1.15 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 1.65 (s, 6H, CC(CH<sub>3</sub>)<sub>2</sub>OH), 1.81 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 2.07 (brs, 1H, OH), 2.72 (s, 4H, 2  $\times$  GeCH<sub>2</sub>NP), 7.04 (dd, *J* = 8.4, 1.7 Hz, 2H, ArH), 7.27 (d, *J* = 7.8 Hz, 2H, ArH), 7.34 (s, 2H, ArH), 7.36-7.46 (m, 6H, ArH), 7.62 (d, *J* = 7.8 Hz, 2H, ArH), 7.67 (d, *J* = 8.4 Hz, 2H, ArH), 7.77 (d, *J* = 7.8 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>)  $\delta$  1.8 (t), 22.4 (2t), 26.2 (t, *J*<sub>CF</sub> = 23.2 Hz), 31.5 (2q), 65.7 (s), 81.9 (s), 94.8 (s), 110.2 (s), 110.6 (2s), 110.7 (s), 110.9 (2s), 111.0 (s), 117.9 (s), 123.6 (s), 124.9 (2d), 125.7 (2d), 126.1 (2d), 127.0 (2d), 127.3 (2d), 127.6 (2d), 128.1 (2d), 131.3 (2d+2s), 133.7 (2d+2s), 136.2 (2s), 137.1 (s); <sup>19</sup>F NMR (376 MHz; CDCl<sub>3</sub>):  $\delta$  -125.2 (s, 2F), -122.6 (s, 2F), -121.8 (s, 2F), -121.0 (m, 6F), -115.4 [quintet, *J* = 14.3 Hz, 2F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>], -79.8 [t, *J* = 9.8 Hz, 3F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>]; IR  $\nu_{\text{max}}$  (neat) 3320 (OH, br), 3054 (C-H), 2985 (C-H), 2354 (CC), 1595 (C=C), 1421 (C-F), 895, 740 cm<sup>-1</sup>; *m/z* (FAB<sup>+</sup>) (rel. intensity) 821 [(M-NpCH<sub>2</sub>)<sup>+</sup>, 55], 551 (50), 279 (45), 141 (100); HRMS (FAB<sup>+</sup>) calc'd. for C<sub>32</sub>H<sub>24</sub>F<sub>17</sub><sup>74</sup>GeO [(M-NapCH<sub>2</sub>)<sup>+</sup>] 821.0767, found 821.0762 ( $\Delta$  -0.6 ppm).

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl) (4-trimethylsilylethynylphenyl)germane 80**



Using Menchi's conditions,  $^{163}Pd(OAc)_2$  (1.0 mg, 0.0045 mmol) and  $PPh_3$  (3.7 mg, 0.014 mmol) were dissolved in DMF (1.0 mL) for 30 min to give a solution of the active Pd(0) catalyst. The catalyst solution was then added to a solution of (4-iodophenyl)germane **78** (25.0 mg, 0.025 mmol) in DMF (2 mL) followed by adding trimethylsilylacetylene (4.9 mg, 0.05 mmol, 7  $\mu$ L), CuI (2 mg, 0.01 mmol) and  $nBuNH_2$  (5 mL). The reaction mixture was then warmed to 55  $^{\circ}C$  for 16 h. The resulting solution was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (3  $\times$  10.0 mL), the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo*. Purification by FC (hexane/EtOAc, 95/5) gave 4-trimethylsilylethynylphenylgermane **80** as a pale yellow oil (12.6 mg, 52 %).  $^1H$  NMR (400 MHz; C<sub>6</sub>D<sub>6</sub>):  $\delta$  0.27 (s, 9H, Si(CH<sub>3</sub>)<sub>3</sub>), 1.02 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 1.71 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 2.36 (s, 4H, 2  $\times$  GeCH<sub>2</sub>NP), 6.86 (dd,  $J$  = 8.4, 1.8 Hz, 2H, ArH), 6.93 (d,  $J$  = 8.1 Hz, 2H, ArH), 7.18-7.20 (m, 3H, ArH), 7.21 (dd,  $J$  = 6.8, 1.4 Hz, 1H, ArH), 7.25 (dd,  $J$  = 6.8, 1.4 Hz, 1H, ArH), 7.27 (dd,  $J$  = 6.8, 1.4 Hz, 1H, ArH), 7.46 (d,  $J$  = 5.5 Hz, 2H, ArH), 7.53 (d,  $J$  = 8.1 Hz, 2H, ArH), 7.59 (d,  $J$  = 8.1 Hz, 2H, ArH);  $^{13}C$  NMR (100.7 MHz; C<sub>6</sub>D<sub>6</sub>)  $\delta$  0.07 (3s), 2.1 (t), 22.5 (2t), 26.6 (t,  $J_{CF}$  = 23.0 Hz), 95.8 (s), 105.6 (s), 105.8 (s), 110.7 (s), 111.2 (s), 111.3 (s), 111.6 (3s), 118.6 (s), 124.7 (s), 125.3 (2d), 126.1 (2d), 126.5 (2d), 127.3 (2d), 127.5 (2d), 128.0 (2d), 128.4 (2d), 131.9 (2d), 132.0 (2s), 134.2 (2d), 134.4 (2s), 136.6 (2s), 138.0 (s);  $^{19}F$  NMR (376 MHz; C<sub>6</sub>D<sub>6</sub>):  $\delta$  -125.1 (s, 2F), -122.3 (s, 2F), -121.7 (s, 2F), -120.8 (m, 4F), -120.3 (s, 2F), -114.9 [quintet,  $J$  = 15.0 Hz, 2F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>], -79.9 [t,  $J$  = 9.8 Hz, 3F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>]; IR  $\nu_{max}$  (neat) 3052 (C-H), 2982 (C-H), 2360 (CC), 1592 (C=C), 1421 (C-F), 1260 (C-Si), 897, 740 cm<sup>-1</sup>;  $m/z$  (FAB<sup>+</sup>) (rel. intensity) 835 [(M-NpCH<sub>2</sub>)<sup>+</sup>, 60], 709 (55), 313 (80), 141 (100); HRMS (FAB<sup>+</sup>) calc'd. for C<sub>32</sub>H<sub>26</sub>F<sub>17</sub><sup>74</sup>GeSi [(M-NapCH<sub>2</sub>)<sup>+</sup>] 835.0739, found 835.0734 ( $\Delta$  -0.6 ppm).

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(naphthalen-2-ylmethyl)(4-phenylethynyl)germane **81****

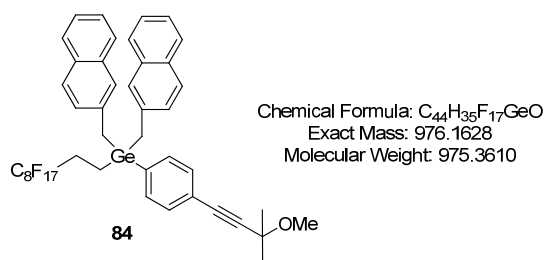


**Method D:** Powdered KOH (50 mg, 0.893 mmol) and 4-((3-methyl-3-hydroxybutynyl)phenyl)germane **79** (80.0 mg, 0.083 mmol) was dissolved in THF (10 mL). The reaction mixture was heated at 80°C for 1 h. The resulting solution was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (3 × 10.0 mL), the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo*. Purification by FC (hexane/EtOAc, 90/10) gave 4-phenylethynylgermane **81** (73.8 mg, 98 %) as pale yellow oil. <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 1.14 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 1.81 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 2.72 (s, 4H, 2 × GeCH<sub>2</sub>NP), 3.15 (s, 1H, C<sub>6</sub>H<sub>4</sub>CCH), 7.04 (dd, *J* = 8.4, 0.8 Hz, 2H, ArH), 7.29 (d, *J* = 8.2 Hz, 2H, ArH), 7.34 (s, 2H, ArH), 7.37-7.48 (m, 6H, ArH), 7.61 (d, *J* = 8.0 Hz, 2H, ArH), 7.68 (d, *J* = 8.4 Hz, 2H, ArH), 7.77 (d, *J* = 7.6 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 2.1 (t), 22.5 (2t), 26.6 (t, *J*<sub>CF</sub> = 23.4 Hz), 78.2 (s), 83.4 (s), 108.3 (s), 110.2 (s), 110.6 (s), 110.9 (3s), 111.0 (s), 117.9 (s), 124.7 (s), 125.3 (2d), 126.1 (2d), 126.5 (2d), 127.4 (2d), 127.4 (2d), 128.0 (2d), 128.3 (2d), 131.8 (2d), 132.0 (2s), 134.3 (2d), 134.3 (2s), 136.5 (2s), 137.8 (s); <sup>19</sup>F NMR (376 MHz; CDCl<sub>3</sub>): δ -125.1 (s, 2F), -122.5 (s, 2F), -121.8 (s, 2F), -121.0 (m, 6F), -115.3 [quintet, *J* = 14.8 Hz, 2F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>], -79.8 [t, *J* = 9.9 Hz, 3F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>]; IR ν<sub>max</sub> (neat) 3253 (CC-H), 3048 (C-H), 2984 (C-H), 2360 (CC), 1592 (C=C), 1420 (C-F), 910, 740 cm<sup>-1</sup>; *m/z* (FAB<sup>+</sup>) (rel. intensity) 763 [(M-NpCH<sub>2</sub>)<sup>+</sup>, 40], 549 (15), 279 (45), 141 (100); HRMS (FAB<sup>+</sup>) calc'd. for C<sub>29</sub>H<sub>18</sub>F<sub>17</sub><sup>74</sup>Ge [M-(NapCH<sub>2</sub>)<sup>+</sup>] 763.0343, found 763.0350 (Δ 0.9 ppm).

**Method E:** To a solution of the (4-trimethylsilylethynylphenyl)germane **80** (115.6 mg, 0.118 mmol) in MeOH-THF (1:1, 10 mL), K<sub>2</sub>CO<sub>3</sub>-KF mixture (1:1, 100 mg) was added and then warmed to 80°C for 8 h. The resulting solution was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (3 × 10.0 mL), the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo*. Purification by FC (hexane/EtOAc,

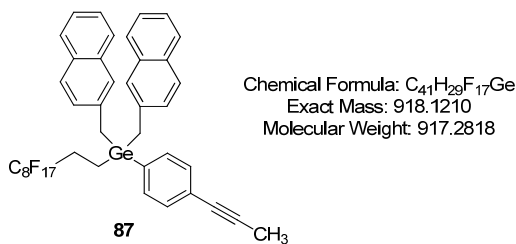
95/5) gave *4-phenylethynylgermane* **81** as pale yellow oil (69.7 mg, 67 %). Analytical data as above.

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl){4-[(3-methyl-3-methoxybutynyl)phenyl]}germane **84****



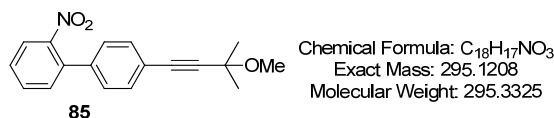
According to Corey's method,<sup>164</sup> to a solution of *germane* **79** (32 mg, 0.0333 mmol) in THF. NaH (4 mg, 0.1 mmol, 60 % in mineral oil). After stirring at RT for 1 h, dimethylsulfate (12.7 mg, 0.1mmol, 9.5  $\mu$ L) was added and the reaction mixture was stirred at RT 16 h. The resulting solution was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (3  $\times$  10.0 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo*. Purification by FC (hexane/EtOAc, 95/5) gave *germane* **84** as pale yellow oil (28.3 mg, 87 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  1.16 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 1.59 (s, 6H, CC(CH<sub>3</sub>)<sub>2</sub>OCH<sub>3</sub>), 1.83 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 2.73 (s, 4H, 2  $\times$  GeCH<sub>2</sub>NP), 3.47 (s, 3H, CC(CH<sub>3</sub>)<sub>2</sub>OCH<sub>3</sub>), 7.04 (dd, *J* = 8.4, 1.8 Hz, 2H, ArH), 7.25-7.29 (m, 2H, ArH), 7.34-7.50 (m, 8H, ArH), 7.63 (d, *J* = 7.7 Hz, 2H, ArH), 7.68 (d, *J* = 8.4 Hz, 2H, ArH), 7.78 (d, *J* = 7.7 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>)  $\delta$  1.8 (t), 22.4 (2t), 26.2 (t, *J*<sub>CF</sub> = 23.0 Hz), 29.7 (2q), 51.7 (q), 70.9 (s), 83.9 (s), 92.1 (s), 108.2 (s), 110.2 (s), 110.6 (2s), 110.94 (2s), 110.98 (s), 117.9 (s), 123.7 (s), 124.9 (2d), 125.7 (2d), 125.8 (s), 126.1 (2d), 127.0 (2d), 127.3 (2d), 127.6 (2d), 128.1 (2d), 131.27 (2s), 131.35 (2d), 133.7 (2d+s), 136.2 (2s), 137.0 (s); <sup>19</sup>F NMR (376 MHz; C<sub>6</sub>D<sub>6</sub>):  $\delta$  -125.1 (s, 2F), -122.6 (s, 2F), -121.8 (s, 2F), -121.0 (m, 6F), -115.4 [quintet, *J* = 14.6 Hz, 2F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>], -79.8 [t, *J* = 9.9 Hz, 3F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>]; IR  $\nu_{\text{max}}$  (neat) 3054 (C-H), 2985 (C-H), 2360 (CC), 1605 (C=C), 1420 (C-F), 912, 740 cm<sup>-1</sup>; *m/z* (FAB<sup>+</sup>) (rel. intensity) 835 [(M-NpCH<sub>2</sub>)<sup>+</sup>, 60], 551 (60), 537 (50), 279 (60), 141 (100); HRMS (FAB<sup>+</sup>) calc'd. for C<sub>33</sub>H<sub>26</sub>F<sub>17</sub>O<sup>74</sup>Ge [M-(NapCH<sub>2</sub>)<sup>+</sup>] 835.0918, found 835.0913 ( $\Delta$  -0.7 ppm).

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(naphthalen-2-ylmethyl)(4-propynylphenyl)germane **87****



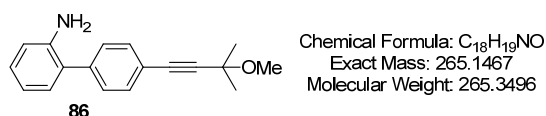
(4-Phenylethynyl)germane **81** (73.8 mg, 0.082 mmol) and DMPU (10.6 mg, 0.083 mmol, 10  $\mu$ L) were dissolved in THF (10 mL) and the solution was cooled to -40 °C. A solution of <sup>n</sup>BuLi (50  $\mu$ L, 0.09 mmol, 1.8 M in hexane ) was added dropwise to the solution and stirred for 1 h at this temperature to give a brown solution. Methyltriflate (20.3 mg, 0.124 mmol, 14  $\mu$ L) was added to the brown solution and stirred for 16 h to give (4-propynylphenyl)germane **87** as pale yellow oil (65.4 mg, 87% ). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  1.21 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 1.80 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ge), 2.08 (s, 3H, CCCH<sub>3</sub>), 2.71 (s, 4H, 2  $\times$  GeCH<sub>2</sub>NP), 7.03 (dd,  $J$  = 8.4, 1.6 Hz, 2H, ArH), 7.23 (d,  $J$  = 8.2 Hz, 2H, ArH), 7.33 (s, 2H, ArH), 7.35-7.42 (m, 6H, ArH), 7.60 (d,  $J$  = 7.8 Hz, 2H, ArH), 7.66 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.76 (d,  $J$  = 7.8 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>):  $\delta$  2.1 (t), 3.2 (q), 22.5 (2t), 26.3 (t,  $J_{CF}$  = 23.2 Hz), 78.3 (s), 83.5 (s), 108.1 (s), 110.2 (s), 110.6 (s), 110.8 (3s), 111.0 (s), 117.9 (s), 124.7 (s), 125.3 (2d), 126.1 (2d), 126.5 (2d), 127.4 (2d), 127.4 (2d), 128.2 (2d), 128.3 (2d), 131.8 (2d), 132.0 (2s), 134.6 (2d), 134.8 (2s), 136.9 (2s), 137.7 (s); <sup>19</sup>F NMR (376 MHz; CDCl<sub>3</sub>):  $\delta$  -126.1 (s, 2F), -123.5 (s, 2F), -122.7 (s, 2F), -121.9 (m, 6F), -116.3 [quintet,  $J$  = 15.2 Hz, 2F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>], -80.7 [t,  $J$  = 9.7 Hz, 3F, (CF<sub>2</sub>)<sub>6</sub>CF<sub>2</sub>CF<sub>3</sub>]; IR  $\nu_{max}$  (neat) 3046 (C-H), 2975 (C-H), 2355 (CC), 1594 (C=C), 1419 (C-F), 913, 740 cm<sup>-1</sup>;  $m/z$  (FAB<sup>+</sup>) (rel. intensity) 777 [(M-NpCH<sub>2</sub>)<sup>+</sup>, 30], 549 (15), 279 (55), 141 (100); HRMS (FAB<sup>+</sup>) calc'd. for C<sub>30</sub>H<sub>20</sub>F<sub>17</sub><sup>74</sup>Ge [M-(NapCH<sub>2</sub>)<sup>+</sup>] 777.0500, found 777.0498 ( $\Delta$  -0.2 ppm).

#### 4-(3-Methyl-3-methoxybutlynyl)-2'-nitrobiphenyl **85**



Using *method C*, the crude difluoroarylgermane from the photolysis of arylgermane **84** (48.9 mg, 0.067 mmol), TBAF (63.0 mg, 0.2 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2 mg, 0.0077 mmol), P(2-Tol)<sub>3</sub> (3.5 mg, 0.012 mmol), 2-bromo-nitrobenzene (27 mg, 0.134 mmol) and CuI (13.3 mg, 0.067 mmol) were employed. Purification by FC (hexane/EtOAc, 90/10) gave 4-(3,3-dimethyl-3-methoxypropynyl)-2'-nitrobiphenyl **85** as a yellow oil (9.9 mg, 50 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 1.56 (s, 6H, 2 × CH<sub>3</sub>), 3.44 (s, 3H, OCH<sub>3</sub>), 7.27 (d, *J* = 6.8 Hz, 2H, ArH), 7.42 (dd, *J* = 7.7, 1.3 Hz, 1H, ArH), 7.48-7.50 (m, 3H, ArH), 7.63 (td, *J* = 7.5, 1.1 Hz, 1H, ArH), 7.88 (dd, *J* = 8.1, 1.0 Hz, 1H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>) δ 28.3 (2q), 51.8 (q), 70.9 (s), 83.7 (s), 92.2 (s), 122.9 (s), 124.2 (d), 127.8 (2d), 128.4 (d), 131.8 (d), 131.9 (2d), 132.0 (s), 132.4 (d), 135.7 (s), 137.2 (s); IR ν<sub>max</sub> (neat) 3055 (C-H), 2987 (C-H), 2360 (CC), 1588 (C=C), 1537 (N=O), 1265 (N=O), 896, 738, 704 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) (rel. intensity) 295 (M<sup>+</sup>, 20), 289 (50), 280 (100), 264 (30), 198 (30); HRMS calc'd. for C<sub>18</sub>H<sub>17</sub>NO<sub>3</sub> 295.1208, found 295.1207 (Δ -0.5 ppm).

#### 4-(3-Methyl-3-methoxybutlynyl)-2'-ylamine biphenyl **86**

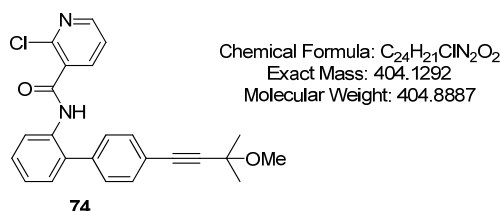


To a solution of 4-(3-methyl-3-methoxybutlynyl)-2'-nitrobiphenyl **85** (9.9 mg, 0.034 mmol) in THF-EtOH (1:1, 10 mL) was added tin(II) chloride (63.7 mg, 0.34 mmol) and conc. HCl (1 mL), the reaction mixture was stirred for 16 h. A sat. solution of K<sub>2</sub>CO<sub>3</sub> was added to the reaction mixture and the reaction mixture was partitioned between Et<sub>2</sub>O (40.0 mL) and water (10.0 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10.0 mL) and dried over MgSO<sub>4</sub>. Purification by FC (hexane/EtOAc, 80/20) gave 4-(3-methyl-3-methoxybutlynyl)-2'-ylaminebiphenyl **86** as a colourless oil (7.1 mg, 80 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 1.56 (s, 6H, 2 × CH<sub>3</sub>), 3.45 (s, 3H, OCH<sub>3</sub>), 3.75 (brs, 2H, NH<sub>2</sub>), 6.77 (dd, *J* = 8.2, 0.7 Hz, 1H, ArH), 6.83 (td, *J* = 7.4, 1.0 Hz, 1H,

ArH), 7.11 (dd,  $J = 7.6, 1.5$  Hz, 1H, ArH), 7.16 (td,  $J = 7.6, 1.5$  Hz, 1H, ArH), 7.42 (d,  $J = 8.3$  Hz, 2H, ArH), 7.51 (d,  $J = 8.3$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  28.4 (2q), 51.7 (q), 71.0 (s), 84.0 (s), 91.4 (s), 115.7 (d), 118.8 (d), 121.6 (s), 126.8 (s), 128.8 (d), 129.0 (2d), 130.3 (d), 132.1 (2d), 139.5 (s), 143.3 (s); IR  $\nu_{\text{max}}$  (neat) 3475 (N-H), 3382 (N-H), 3052 (C-H), 3021 (C-H), 2280 (CC), 1887 (comb), 1617 (C=C), 1472, 810, 743  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 265 ( $\text{M}^+$ , 85), 250 (100), 234 (50), 220 (40), 125 (30); HRMS calc'd. for  $\text{C}_{18}\text{H}_{19}\text{NO}$  265.1467, found 265.1464 ( $\Delta$  -1.0 ppm).

## 2-Chloro-*N*-[4'-(3-methoxy-3-methylbut-1-ynyl)biphenyl-2-yl] nicotinamide

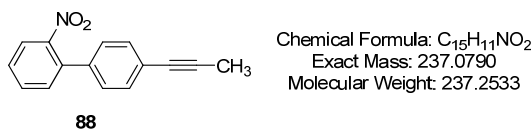
**74**<sup>162</sup>



To a solution of 4-(3-methyl-3-methoxybutynyl)-2'-ylaminebiphenyl **86** (12 mg, 0.045 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added 2-chloro-3-nicotinic acid (7.2 mg, 0.045 mmol), DMAP (0.6 mg, 0.0049 mmol) and DCC (10.3 mg, 0.050 mmol), the reaction mixture was stirred for 16 h. A sat. solution of  $\text{K}_2\text{CO}_3$  was added to the reaction mixture and the reaction mixture was partitioned between  $\text{Et}_2\text{O}$  (40.0 mL) and water (10.0 mL), extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10.0$  mL) and dried over  $\text{MgSO}_4$ . Purification by FC (hexane/ $\text{EtOAc}$ , 70/30) gave *alkyne* **74** as a colourless oil (12.5 mg, 68 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.56 (s, 6H,  $2 \times \text{CH}_3$ ), 3.44 (s, 3H,  $\text{OCH}_3$ ), 7.27 (d,  $J = 6.3$  Hz, 2H, ArH), 7.34-7.38 (m, 3H, ArH), 7.46 (td,  $J = 8.6, 2.8$  Hz, 1H, ArH), 7.52 (d,  $J = 8.2$  Hz, 2H, ArH), 8.14 (dd,  $J = 7.7, 1.9$  Hz, 1H, ArH), 8.16 (brs, 1H, NH), 8.44-8.46 (m, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  28.3 (2q), 51.8 (q), 70.9 (s), 83.5 (s), 92.2 (s), 121.8 (d), 122.90 (d), 122.93 (s), 125.2 (d), 128.2 (d), 129.4 (2d), 130.1 (d), 131.1 (s), 132.4 (2d), 132.6 (s), 134.3 (s), 137.6 (s), 140.1 (d), 146.7 (s), 151.3 (d), 162.5 (s); IR  $\nu_{\text{max}}$  (neat) 3325 (N-H), 3053 (C-H), 2931 (C-H), 2341 (CC), 1654 (C=O), 1578 (C=C), 1070, 734  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{CI}^+$ ) (rel. intensity) 424 [ $(\text{M}^{37}\text{Cl}) + \text{NH}_4^+$ , 1], 422 [ $(\text{M}^{37}\text{Cl}) + \text{NH}_4^+$ , 3], 390 (40), 373 (100), 339 (20), 225

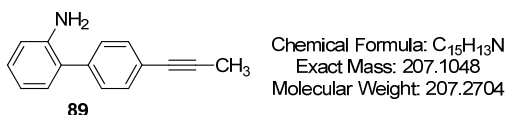
(50); HRMS ( $\text{Cl}^+$ ) calc'd. for  $\text{C}_{24}\text{H}_{25}\text{ClN}_3\text{O}_2$   $[\text{M}+\text{NH}_4]^+$  422.1635, found 422.1633 ( $\Delta$  -0.5 ppm).

#### 4-Propynyl-2'-nitrobiphenyl **88**



Using *method C*, the crude difluoroarylgermane from the photolysis of arylgermane **87** (33.2 mg, 0.049 mmol), TBAF (46.6 mg, 0.148 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (1.5 mg, 0.0058 mmol),  $\text{P}(2\text{-Tol})_3$  (2.6 mg, 0.0087 mmol), 2-bromo-nitrobenzene (19.9 mg, 0.099 mmol) and CuI (9.8 mg, 0.049 mmol) were employed. Purification by FC (hexane/EtOAc, 90/10) to give 4-propynyl-2'-nitrobiphenyl **88** as a pale yellow oil (6.3 mg, 54%).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.07 (s, 3H,  $\text{CH}_3$ ), 7.24 (d,  $J = 7.0$ , 2H, ArH), 7.41-7.48 (m, 3H, ArH), 7.48 (td,  $J = 7.9$ , 1.4 Hz, 1H, ArH), 7.62 (td,  $J = 7.5$ , 1.1 Hz, 1H, ArH), 7.86 (dd,  $J = 8.1$ , 1.1 Hz, 1H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  4.4 (q), 79.2 (s), 87.1 (s), 124.1 (s), 124.2 (d), 127.8 (2d), 128.3 (d), 131.77 (2d), 131.8 (d), 132.3 (d), 135.8 (s), 136.4 (s), 149.1 (s); IR  $\nu_{\text{max}}$  (neat) 3054 (C-H), 2987 (C-H), 2360 (CC), 1588 (C=C), 1537 (N=O), 1265 (N=O), 896, 738, 705  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 237 ( $\text{M}^+$ , 20), 198 (100), 168 (50), 87 (70); HRMS calc'd. for  $\text{C}_{15}\text{H}_{11}\text{NO}_2$  237.0790, found 237.0784 ( $\Delta$  -2.4 ppm).

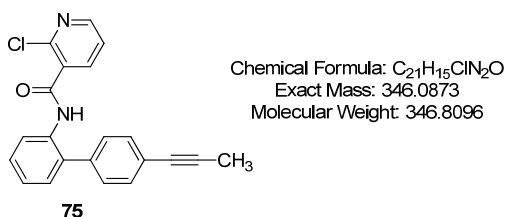
#### 4-Propynyl-2'-ylaminebiphenyl **89**



To a solution of 4-propynyl-2'-nitrobiphenyl **88** (6.3 mg, 0.027 mmol) in THF-EtOH (1:1, 10 mL) was added tin(II) chloride (50.1 mg, 0.27 mmol) and conc. HC (1 mL) and the reaction mixture was stirred for 16 h. A sat. solution of  $\text{K}_2\text{CO}_3$  was added to the reaction mixture and the reaction mixture was partitioned between  $\text{Et}_2\text{O}$  (40.0 mL) and water (10.0 mL), extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10.0$  mL) and dried over  $\text{MgSO}_4$ . Purification by FC (hexane/EtOAc, 90/10) gave

4-propynyl-2'-ylaminebiphenyl **89** as a colourless oil (4.4 mg, 80 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.08 (s, 3H,  $\text{CH}_3$ ), 3.76 (brs, 2H,  $\text{NH}_2$ ), 6.76 (d,  $J = 7.9$  Hz, 1H, ArH), 6.82 (t,  $J = 7.3$  Hz, 1H, ArH), 7.11 (dd,  $J = 7.5, 1.2$  Hz, 1H, ArH), 7.16 (td,  $J = 7.8, 1.4$  Hz, 1H, ArH), 7.39 (d,  $J = 8.2$  Hz, 2H, ArH), 7.46 (d,  $J = 8.2$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  4.4 (q), 86.3 (s), 102.3 (s), 115.8 (d), 118.8 (d), 119.1 (s), 122.9 (s), 128.7 (d), 128.9 (2d), 130.3 (d), 131.9 (2d), 138.7 (s), 144.5 (s); IR  $\nu_{\text{max}}$  (neat) 3475 (N-H), 3384 (N-H), 3052 (C-H), 2984 (C-H), 2359 (CC), 1888 (comb), 1616 (C=C), 1472, 817, 738, 704  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity) 207 (100), 167 (40), 149 (85), 57 (65); HRMS calc'd. for  $\text{C}_{15}\text{H}_{13}\text{N}$  207.1048, found 207.1050 ( $\Delta$  -1.0 ppm).

## 2-Chloro-*N*-(4'-prop-1-ynylbiphenyl-2-yl)nicotinamide **75**<sup>162</sup>



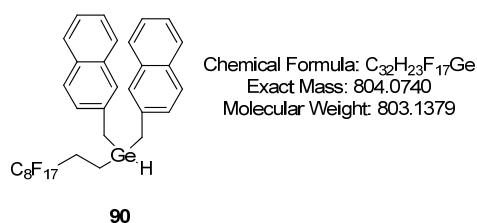
To a solution of 4-(3-methyl-3-methoxybutynyl)-2'-ylaminebiphenyl **89** (4.5 mg, 0.022 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added 2-chloro-3-nicotinic acid (6.9 mg, 0.042 mmol), DMAP (0.5 mg, 0.004 mmol) and DCC (10.0 mg, 0.048 mmol) and the reaction mixture was stirred for 16 h. A sat. solution of  $\text{K}_2\text{CO}_3$  was added to the reaction mixture and the reaction mixture was partitioned between  $\text{Et}_2\text{O}$  (40.0 mL) and water (10.0 mL), extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10.0$  mL) and dried over  $\text{MgSO}_4$ . Purification by FC (hexane/ $\text{EtOAc}$ , 70/30) gave *alkyne* **75** as a colourless oil (4.4 mg, 59 %).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.07 (s, 3H,  $\text{CH}_3$ ), 7.27 (d,  $J = 6.5$  Hz, 2H, ArH), 7.33-7.39 (m, 3H, ArH), 7.46 (td,  $J = 8.4, 1.6$  Hz, 1H, ArH), 7.50 (d,  $J = 8.2$  Hz, 2H, ArH), 8.12 (dd,  $J = 7.5, 1.9$  Hz, 1H, ArH), 8.15 (brs, 1H, NH), 8.42-8.44 (m, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ )  $\delta$  4.3 (q), 86.2 (s), 93.1 (s), 121.6 (d), 122.8 (d), 122.9 (s), 125.0 (d), 128.0 (d), 129.2 (2d), 130.1 (d), 131.0 (s), 132.2 (2d), 132.4 (s), 134.3 (s), 137.4 (s), 140.0 (d), 146.5 (s), 151.1 (d), 162.3 (s); IR  $\nu_{\text{max}}$  (neat) 3325 (N-H), 3053 (C-H), 2935 (C-H), 2305 (CC), 1654 (C=O), 1580 (C=C), 1265, 735  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{CI}^+$ ) (rel. intensity) 349 [ $(\text{M}^{37}\text{Cl}) + \text{H}^+$ , 5], 347 [ $(\text{M}^{35}\text{Cl}) + \text{H}^+$ , 15],

328 (40), 225 (100); HRMS ( $\text{Cl}^+$ ) calc'd. for  $\text{C}_{21}\text{H}_{16}\text{ClN}_2\text{O}$   $[\text{M}+\text{H}]^+$  347.0951, found 347.0952 ( $\Delta$  1.3 ppm).

### *Scope of alkenyl germyl-Stille cross-coupling reaction*

*Preparation of Rf-tagged alkenyl germanes:*

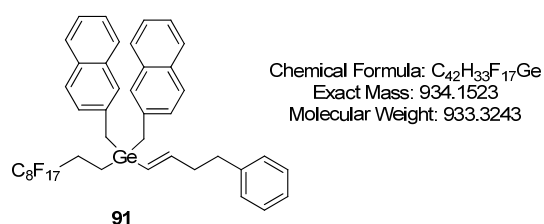
#### **(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl)germane **90****



To a solution of bromogermane **40** (0.250 g, 0.283 mmol) in THF (20.0 mL) at 0 °C was added  $\text{LiEt}_3\text{BH}$  (0.30 mL, 0.30 mmol, 1 M) dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 4 h. The reaction mixture was then quenched with  $\text{NaHCO}_3$ , and extracted with  $\text{Et}_2\text{O}$  ( $2 \times 10.0$  mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$ , and the solvent evaporated *in vacuo*. Purification by FC eluting with (hexane/ $\text{EtOAc}$ , 95/5) followed by recrystallisation from hexane yielded *germane 90* as a white crystalline solid (0.160 g, 70%). mp. 63-68 °C;  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  1.03 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 1.90 (m, 2H,  $\text{CH}_2\text{CH}_2\text{Ge}$ ), 2.54 (dd,  $J = 12.8, 2.9$  Hz, 2H,  $\text{GeCH}_2\text{Nap}$ ), 2.59 (dd,  $J = 12.8, 2.9$  Hz, 2H,  $\text{GeCH}_2\text{Nap}$ ), 4.27 (br s, 1H, Ge-H), 7.17 (dd,  $J = 8.5$  and 2.0 Hz, 2H, ArH), 7.36-7.45 (m, 6H, ArH), 7.68 (d,  $J = 8.5$  Hz, 2H, ArH), 7.73 (d,  $J = 8.5$  Hz, 2H, ArH), 7.78 (dd,  $J = 6.5, 2.0$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100MHz;  $\text{CDCl}_3$ ):  $\delta$  1.6 (t), 21.3 (2t), 27.4 (t,  $J_{\text{CF}} = 23.1$  Hz), 108.2 (s), 110.2 (s), 110.6 (2s), 110.9 (2s), 111.2 (s), 117.9 (s), 124.9 (2d), 125.4 (2d), 126.1 (2d), 127.0 (2d), 127.1 (2d), 127.6 (2d), 128.3 (2d), 131.3 (2s), 133.8 (2s), 137.2 (2s);  $^{19}\text{F}$  NMR (376MHz;  $\text{CDCl}_3$ ):  $\delta$  -125.1 (s, 2F), -122.7 (s, 2F), -121.8 (s, 2F), -121.0 (s, 4F,  $2 \times \text{CF}_2$ ), -120.9 (s, 2F), -115.3 (quintet,  $J = 15.0$  Hz, 2F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ), -78.8 (t,  $J = 10.0$  Hz, 3F,  $(\text{CF}_2)_6\text{CF}_2\text{CF}_3$ ); IR  $\nu_{\text{max}}$  (neat): 3055, 2925, 1540, 1195, 1145, 905, 820  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ) (rel. intensity)

804 ( $M^+$ , 18), 531 (11), 215 (45), 141 (100); HRMS calc'd. for  $C_{32}H_{23}F_{17}^{74}Ge$  ( $M^+$ ) 804.0740, found 804.0737 ( $\Delta$  -0.4 ppm).

**(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl)[(E)-4-phenylbut-1-enyl]germane **91****



**Method 1:**

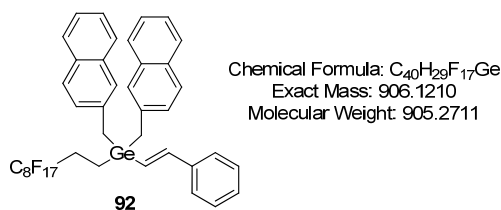
According to the method of Wada's,<sup>175</sup> to a solution of germane **90** (0.050 g, 0.062 mmol) in  $CH_2Cl_2$  (10.0 mL) was added galvinoxyl (0.025 g, 0.062 mmol),  $(Ph_3P)_2Rh(CO)Cl$  (1.0 mg, 0.001 mmol) and 4-phenyl-1-butyne (80  $\mu$ L, 0.620 mmol). The reaction mixture was refluxed at 40°C for 20 h. The reaction mixture was then quenched with  $NaHCO_3$ , and extracted with  $CH_2Cl_2$  ( $2 \times 10.0$  mL). The combined organic extracts were dried over  $Na_2SO_4$ , and the solvent evaporated *in vacuo*. Purification by FC eluting with (hexane/EtOAc, 99/1) yielded crude (E)-4-phenylbut-1-enyl]germane **91** as a yellow oil (0.080 g) and inseparable galvinoxyl derivatives.  $^1H$  NMR (400MHz;  $CDCl_3$ ):  $\delta$  1.00 (m, 2H,  $CH_2CH_2Ge$ ), 1.88 (m, 2H,  $CH_2CH_2Ge$ ), 2.47 (d,  $J = 7.1$  Hz, 1H,  $GeCH=CHCH_2CH_2Ph$ ), 2.51 (d,  $J = 7.1$  Hz, 1H,  $GeCH=CHCH_2CH_2Ph$ ), 2.54 (s, 4H,  $2 \times GeCH_2Nap$ ), 2.71 (t,  $J = 7.0$  Hz, 2H,  $GeCH=CHCH_2CH_2Ph$ ), 5.70 (d,  $J = 18.5$  Hz, 1H,  $GeCH=CH(CH_2)_2Ph$ ), 6.01 (dt,  $J = 18.5, 7.0$  Hz, 1H,  $GeCH=CH(CH_2)_2Ph$ ), 7.15 (d,  $J = 8.5$  Hz, 2H, ArH), 7.23-7.34 (m, 5H, ArH), 7.43-7.50 (m, 6H, ArH), 7.71 (d,  $J = 8.0$  Hz, 2H, ArH), 7.75 (d,  $J = 8.5$ Hz, 2H, ArH), 7.83 (d,  $J = 8.0$ Hz, 2H, ArH);  $^{13}C$  NMR (100MHz;  $CDCl_3$ ):  $\delta$  2.3 (t), 22.7 (t), 26.4 (t,  $J_{CF} = 23.5$  Hz), 108.2 (s), 110.2 (s), 110.6 (2s), 110.8 (2s), 111.0 (s), 117.9 (s), 124.5 (d), 124.7 (2d), 125.5 (2d), 125.9 (d), 126.0 (2d), 127.0 (2d), 127.6 (2d), 128.0 (2d), 128.1 (2d), 128.3 (2d), 128.4 (2d), 131.2 (2s), 133.7 (2s), 135.7 (s), 137.0 (s), 141.3 (s), 148.2 (d);  $^{19}F$  NMR (376MHz;  $CDCl_3$ ):  $\delta$  -126.1 (s, 2F), -123.4 (s, 2F), -122.7 (s, 2F), -121.9 (s, 6F,  $3 \times CF_2$ ), -116.2 (quintet,  $J = 14.0$ Hz, 2F,  $(CF_2)_6CF_2CF_3$ ), -80.7 (t,  $J = 10.0$  Hz, 3F,  $(CF_2)_6CF_2CF_3$ ); IR  $\nu_{max}$  (neat): 3055,

2925, 1630, 1505, 1440, 1240, 1210, 1150, 890, 820  $\text{cm}^{-1}$ ;  $m/z$  (FAB<sup>+</sup>) (rel. intensity) 793 [30, (M-CH<sub>2</sub>Np)<sup>+</sup>], 719 (10), 365 (20), 291 (20), 141 (100); HRMS calc'd. for C<sub>31</sub>H<sub>24</sub>F<sub>17</sub>Ge [(M-NapCH<sub>2</sub>)<sup>+</sup>] 793.0818, found 793.0799 ( $\Delta$  -2.4 ppm).

## Method 2:

To a solution of germane **90** (0.50 g, 0.62 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25.0 mL) was added (Ph<sub>3</sub>P)<sub>2</sub>Rh(CO)Cl (12.9 mg, 0.019 mmol) and 4-phenyl-1-butyne (0.8 mL, 6.2 mmol). The reaction mixture was refluxed at 40 °C for 24 h. The reaction mixture was then quenched with NaHCO<sub>3</sub>, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10.0 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent evaporated *in vacuo*. Purification by FC eluting with (hexane/EtOAc, 99/1) gave (*E*)-4-phenylbut-1-enyl]germane **91** as a yellow oil (0.56 g, 96 %). Analytical data as shown above.

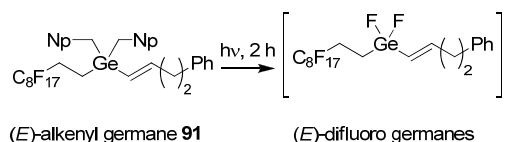
## (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)bis(naphthalen-2-ylmethyl)[(*E*)-styrenyl]germane **92**



To a solution of germane **90** (0.32g, 0.398 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL) was added (Ph<sub>3</sub>P)<sub>2</sub>Rh(CO)Cl (8.2 mg, 0.012 mmol) and phenylacetylene (0.44 mL, 4.0 mmol). The reaction mixture was refluxed at 40°C for 24 h. The reaction mixture was then quenched with NaHCO<sub>3</sub>, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10.0 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent evaporated *in vacuo*. Purification by FC eluting with pet. ether 40-60 °C/Et<sub>2</sub>O (98:2) gave (*E*)-styrenyl germane **92** as a yellow oil (0.317 g, 88 %). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  1.07-1.11 (m, 2H, C<sub>8</sub>F<sub>17</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 1.87-1.97 (m, 2H, C<sub>8</sub>F<sub>17</sub>CH<sub>2</sub>CH<sub>2</sub>Ge), 2.65 (s, 4H, GeCH<sub>2</sub>Np), 6.50 (d,  $J$  = 19.0 Hz, 1H, GeCH=CHPh), 6.81 (d,  $J$  = 19.0 Hz, 1H, GeCH=CHPh), 7.19 (dd,  $J$  = 8.4, 1.4 Hz, 2H, ArH), 7.34-7.37 (m, 5H, ArH), 7.40-7.48 (m, 6H, ArH), 7.68 (d,  $J$  = 7.8 Hz, 2H, ArH), 7.74 (d,  $J$  = 8.4 Hz, 2H, ArH),

7.81 (d,  $J = 7.8$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.5 (t), 22.2 (2t), 26.7 (t,  $J_{\text{CF}} = 23.2$  Hz), 108.4 (s), 110.2 (s), 110.7 (2s), 111.0 (2s), 111.1 (s), 118.0 (s), 126.4 (2d), 127.0 (2d), 127.4 (2d), 127.6 (2d), 128.1 (2d), 128.4 (d), 128.6 (2d), 131.3 (2s), 133.8 (2s), 136.7 (2s), 137.5 (s), 145.7 (d);  $^{19}\text{F}$  NMR (376MHz;  $\text{CDCl}_3$ ):  $\delta$  -125.1 (s, 2F), -122.5 (s, 2F), -121.8 (s, 2F), -120.9 (m, 6F), -115.2 (quintet,  $J = 14.6$  Hz, 2F), -79.9 (t,  $J = 9.6$  Hz, 3F); IR  $\nu_{\text{max}}$  (neat): 3055, 3020, 2920, 1630, 1600, 1510, 1240, 1210, 1150, 855, 820  $\text{cm}^{-1}$ ;  $m/z$  (FAB $^{+}$ ) (rel. intensity) 765 [5, (M-CH $_2$ Np) $^{+}$ ], 662 (3), 521 (5), 141 (100), 104 (20) HRMS calc'd. for  $\text{C}_{29}\text{H}_{20}\text{F}_{17}\text{Ge}$  [(M-NapCH $_2$ ) $^{+}$ ] 765.0505, found 765.0517 ( $\Delta$  1.6 ppm).

***General procedure for photolysis of alkenylgermanes:***



To a solution of the *alkenylgermanes* (0.102 mmol) in MeCN/MeOH (3/1 v/v, 20 mL) in a Pyrex Schlenk tube (1 mm thick) was added powdered  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$  (0.408 mmol). The resulting mixture was purged with argon for 30 min before irradiating using a 125 W high pressure Hg lamp for 1 h. A further portion of powdered  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$  (0.408 mmol) was then added and the solution irradiated for a further 1 h. After this time, the solvent was removed *in vacuo*, the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (20.0 mL), washed with water ( $2 \times 8.0$  mL) and dried over  $\text{MgSO}_4$  to give the crude *difluoroalkenylgermane*.  $^1\text{H}$  NMR spectrum of the crude reaction mixture displayed an 18.5 Hz vicinal alkenyl coupling constant indicating no photoinduced double bond isomerisation occurred. Additionally,  $^{19}\text{F}$  NMR revealed three signals at  $\delta$  -165 ~ -162 ppm. These were assigned as activated difluorogermane derivatives as for the arylgermane analogues (see discussion section 2.6.1.2).

**General method for cross-coupling of photoactivated alkenylgermanes with aryl bromides:**

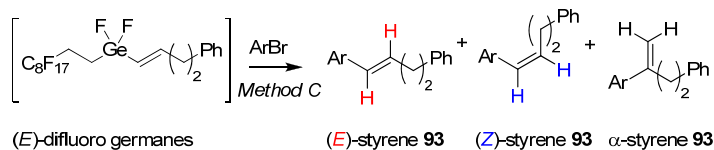
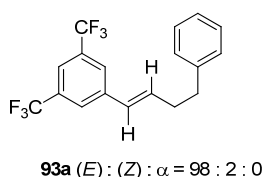


**Table 2.6.9, entry 1: (E)-1-(3-(3,5-Bis(trifluoromethyl)phenyl)but-3-enyl)benzene **93a****



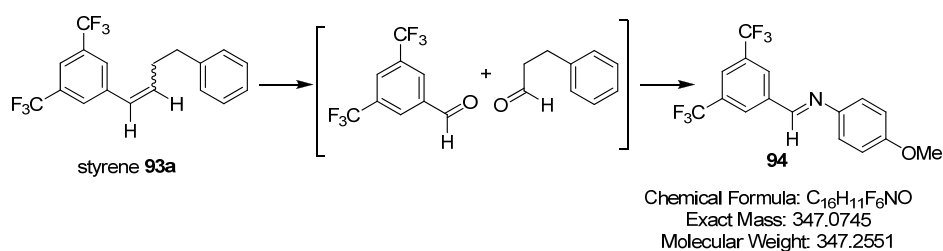
**Method C:** The crude difluoroalkenylgermane from the photolysis of arylgermane **91** (70.3 mg, 0.102 mmol) for 2 h with 4 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$  and TBAF (96.4 mg, 0.306 mmol) was dissolved in degassed DMF (2 mL) and stirred for 30 min.  $\text{PdCl}_2(\text{MeCN})_2$  (2.6 mg, 0.0102 mmol) and  $\text{P}(2\text{-Tol})_3$  (4.7 mg, 0.0153 mmol) were dissolved in degassed DMF (1 mL) for 30 min to form the active catalytic species. The catalyst solution was added to the difluoroalkenylgermane solution followed by adding 3,5-bis(trifluoromethyl)-bromobenzene (59.8 mg, 0.204 mmol, 35.2  $\mu\text{L}$ ) and  $\text{CuI}$  (20.3 mg, 0.102 mmol). The resulting mixture was heated at 120  $^\circ\text{C}$  for 16 h under nitrogen atmosphere. The crude reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20.0 mL) and washed with water ( $3 \times 10.0$  mL), the combined organic extracts were dried over  $\text{MgSO}_4$  and evaporated *in vacuo*. Purification by FC (hexane/ $\text{EtOAc}$ , 97/3) gave *styrene 93a* as a pale yellow oil (22.8 mg, 65 %). Although the isomers could not be separated and authentic sample was not available, the ratio of the isomers was identified by a combination of GC-MS and  $^1\text{H}$  NMR spectroscopic analysis as being (E) : (Z) : ( $\alpha$ ) = 98 : 2 : 0 mixture of isomers.

**(E)-isomer:**  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.58 (dt,  $J = 12.8, 6.4$  Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 2.61 (dt,  $J = 12.8, 6.4$  Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 2.82 (t,  $J = 7.0$  Hz, 2H,  $\text{CH}_2\text{Ph}$ ), 6.43-6.46 (m, 2H,  $\text{CH}=\text{CHCH}_2$ ), 7.21-7.33 (m, 5H, ArH), 7.69 (s, 1H, ArH), 7.72 (s, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ ):  $\delta$  34.8 (t), 35.4 (t), 120.4 (d), 123.4 (2s,  $^1J_{\text{C-F}} = 272.8$  Hz,  $2 \times \text{CF}_3$ ), 125.8 (2d), 126.1 (d), 128.0 (d), 128.4 (2d), 128.5 (2d), 131.8 (2s,  $^2J_{\text{C-F}} = 32.7$  Hz), 134.3 (d), 139.7 (s), 141.2 (s);  $^{19}\text{F}$  NMR

(376MHz; CDCl<sub>3</sub>):  $\delta$  -63.0 (s, 6F, 2  $\times$  CF<sub>3</sub>); IR  $\nu_{\max}$  (neat): 3025, 2930, 1650, 1500, 1380, 1280, 1175, 1135 965, 895 cm<sup>-1</sup>; GC/MS retention time 9.68 min;  $m/z$  (EI<sup>+</sup>) 344 (M<sup>+</sup>, 30), 325 (20), 253 (20), 115 (10), 91 (100); HRMS calc'd. for C<sub>18</sub>H<sub>14</sub>F<sub>6</sub> 344.1000, found 344.0995 ( $\Delta$  -1.4 ppm).

**(Z)-isomer:** GC/MS retention time 10.87 min,  $m/z$  (EI<sup>+</sup>) 344 (M<sup>+</sup>, 20), 325 (10), 253 (40), 115 (40), 91 (100).

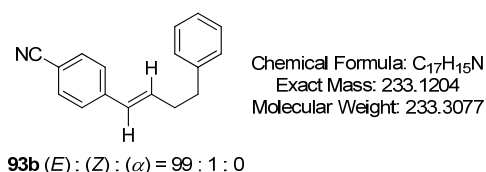
*Ozonolysis of styrene 93a for determination of double bond regiochemistry*



**(E)-N-(3,5-bis(trifluoromethyl)benzylidene)-4-methoxybenzenamine 94**

To a solution of styrene **93a** (16 mg, 0.046 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was cooled to -78 °C and purged with ozone until a blue colour solution was observed. The mixture was then warmed up to RT for 10 min followed by addition of PPh<sub>3</sub> (30.5 mg, 0.016 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and stirred for 1 h after which 4-ansidine (14.3 mg, 0.116mmol) was charged into the reaction mixture at this temperature for another 2 h. The resulting mixture was quenched with sat. NaHCO<sub>3</sub> and extraction with (2  $\times$  20.0 mL) of Et<sub>2</sub>O, the combined organic extracts were dried over MgSO<sub>4</sub> and evaporated *in vacuo* to give yellow residue which was purified by FC (hexane/EtOAc, 80/20) to give imine **94** (12.5 mg, 78 %) as a pale yellow solid. mp. 78-79 °C; <sup>1</sup>H NMR (400 MHz):  $\delta$  3.85 (s, 3H, OCH<sub>3</sub>), 6.97 (dd,  $J$  = 8.8, 1.2 Hz, 2H, ArH), 7.31 (dd,  $J$  = 8.8, 1.2 Hz, 2H, ArH), 7.94 (br s, 1H ArH), 8.35 (br s, 2H, ArH), 8.58 (s, 1H, CH=N); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>):  $\delta$  55.5 (q), 114.6 (2d), 122.5 (2d), 123.1 (2s, <sup>1</sup> $J_{C-F}$  = 266 Hz, 2  $\times$  CF<sub>3</sub>), 123.9 (d), 128.2 (2d), 132.2 (2s, <sup>2</sup> $J_{C-F}$  = 34.1 Hz), 138.4 (s), 143.3 (s), 153.9 (d), 159.2 (s); IR  $\nu_{\max}$  (neat): 3025, 2960, 2840, 1630, 1510, 1280, 1170, 1130, 1025. 830 cm<sup>-1</sup>;  $m/z$  (EI<sup>+</sup>) 347 (M<sup>+</sup>, 100), 332 (90), 303 (30), 235 (30), 134 (20), 92 (20); HRMS calc'd. for C<sub>16</sub>H<sub>11</sub>F<sub>6</sub>NO 347.0745, found 347.0741 ( $\Delta$  -1.1 ppm).

Table 2.6.9, entry 2: **4-((*E*)-4-Phenylbut-1-enyl)benzonitrile 93b**

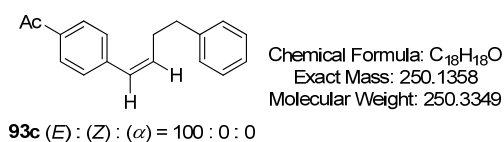


Using *method C*, the crude difluoro alkenylgermane (70.3 mg, 0.102 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (96.4 mg, 0.306 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.6 mg, 0.0102 mmol), P(2-Tol)<sub>3</sub> (4.7 mg, 0.0153 mmol), 4-cyanobromobenzene (37.1 mg, 0.204 mmol) and CuI (20.3 mg, 0.102 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *styrene 93b* as a (*E*) : (*Z*) : ( $\alpha$ ) = 99 : 1 : 0 mixture of isomers (15.4 mg, 65 %) as a pale yellow solid.

**(*E*)-isomer**: mp. 52-53 °C; <sup>1</sup>H NMR (400 MHz):  $\delta$  2.55-2.62 (m, 2H, CH=CHCH<sub>2</sub>), 2.83 (t, *J* = 7.7 Hz, 2H, CH<sub>2</sub>Ph), 6.40-6.43 (m, 2H, CH=CHCH<sub>2</sub>), 7.22-7.30 (m, 3H, ArH), 7.40-7.51 (m, 2H, ArH), 7.54 (d, *J* = 8.6 Hz, 2H, ArH), 7.65 (d, *J* = 8.6 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>):  $\delta$  35.0 (t), 35.7 (t), 126.1 (3d), 128.5 (2d), 128.7 (2d), 128.9 (2d), 129.5 (d), 133.2 (d), 135.7 (s), 141.4 (s), 141.9 (s), 142.4 (s); IR  $\nu_{\text{max}}$  (neat): 3025, 2920, 2230, 1695, 1610, 1455, 825 cm<sup>-1</sup>; GC/MS retention time 12.52 min, *m/z* (EI<sup>+</sup>) 233 (M<sup>+</sup>, 30), 141 (40), 115 (20), 91 (100); HRMS calc'd. for C<sub>17</sub>H<sub>15</sub>N 233.1204, found 233.1204 ( $\Delta$  0 ppm).

**(*Z*)-isomer**: GC/MS retention time 11.98 min, *m/z* (EI<sup>+</sup>) 233 (M<sup>+</sup>, 5), 141 (10), 115 (10), 91 (100).

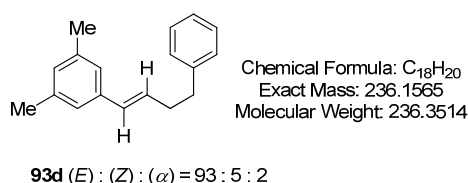
Table 2.6.9, entry 3: **1-(4-((*E*)-4-Phenylbut-1-enyl)phenyl)ethanone 93c**



Using *method C*, the crude difluoro alkenylgermane (70.3 mg, 0.102 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (96.4 mg, 0.306 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.6 mg, 0.0102 mmol), P(2-Tol)<sub>3</sub> (4.7 mg, 0.0153 mmol), 4-bromoacetophenone (40.6 mg, 0.204 mmol) and CuI (20.3 mg,

0.102 mmol) were employed. Purification by FC (hexane/EtOAc, 90/10) gave *styrene 93c* as a single isomer (15.1 mg, 59 %) as a pale yellow solid. mp. 55-56 °C <sup>1</sup>H NMR (400 MHz): δ 2.53-2.59 (m, 5H, CH=CHCH<sub>2</sub>+COCH<sub>3</sub>), 2.81 (t, *J* = 7.7 Hz, 2H, CH<sub>2</sub>Ph), 6.35-6.48 (m, 2H, CH=CHCH<sub>2</sub>), 7.20-7.23 (m, 3H, ArH), 7.27-7.33 (m, 2H, ArH), 7.40 (d, *J* = 8.3 Hz, 2H, ArH), 7.89 (d, *J* = 8.3 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>): δ 26.6 (q), 35.0 (t), 35.6 (t), 126.0 (3d), 128.4 (2d), 128.5 (2d), 128.8 (2d), 129.6 (d), 133.2 (d), 135.6 (s), 141.4 (s), 142.3 (s), 197.6 (s); IR ν<sub>max</sub> (neat): 3085, 2930, 1675, 1600, 1270, 910, 855, 810 cm<sup>-1</sup>; *m/z* (EI<sup>+</sup>) 250 (M<sup>+</sup>, 40), 207 (10), 159 (20), 115 (20), 90 (50), 43 (100); HRMS calc'd. for C<sub>18</sub>H<sub>18</sub>O 250.1358, found 250.1362 (Δ 1.7 ppm).

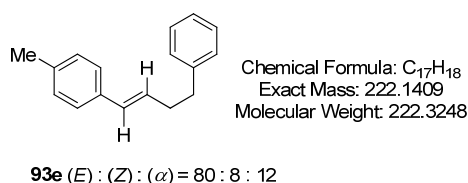
Table 2.6.9, entry 4: **1,3-Dimethyl-5-(4-phenylbut-1-enyl)benzene 93d**



Using *method C*, the crude difluoro alkenylgermane (85.0 mg, 0.123 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (116.6 mg, 0.370 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (3.2 mg, 0.0123 mmol), P(2-Tol)<sub>3</sub> (5.6 mg, 0.0185 mmol), 1-bromo-3,5-dimethylbenzene (45.5 mg, 0.246 mmol, 33.4 μL) and CuI (24.5 mg, 0.123 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *styrene 93d* as a (*E*) : (*Z*) : (α) = 93 : 5 : 2 mixture of isomers (18.3 mg, 63 %) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz): δ 2.34 [(*E*)+(*Z*)+(α)] (3 × s, 6H, 2 × CH<sub>3</sub>), 2.43-2.50 (*E*) and 2.57-2.65 [(*Z*)+(α)] (m, 2H, CH=CHCH<sub>2</sub>), 2.81-2.87 [(*E*)+(*Z*)+(α)] (m, 2H, CH<sub>2</sub>Ph), 5.09 (α) (s, 1H, =CH), 5.33 (α) (s, 1H, =CH), 6.29 (*E*) and 6.26-6.31 (*Z*) (dt and m, *J* = 15.8, 6.7 Hz, 1H, CH=CHCH<sub>2</sub>), 6.41 (*E*) and 6.44-6.47 (*Z*) (d and m, *J* = 15.8 Hz, 1H, CH=CHCH<sub>2</sub>), 6.91 [(*E*)+(*Z*)+(α)] (s, 1H, ArH), 7.02 [(*E*)+(*Z*)+(α)] (s, 2H, ArH), 7.35-7.39 [(*E*)+(*Z*)+(α)] (m, 2H, ArH), 7.44-7.52 [(*E*)+(*Z*)+(α)] (m, 3H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>): [(*E*)+(*Z*)+(α)] δ 20.5 (q), 20.7 (q), 30.5 (t), 34.8 (t), 35.9 (t), 36.1 (t), 122.5 (d), 125.9 (d), 128.3 (d), 128.4 (d), 128.7 (d), 129.2 (s), 134.7 (s), 136.5 (s), 138.2 (s); IR ν<sub>max</sub> (neat): 3040, 1790,

1380, 1275, 1170, 1130, 960, 895  $\text{cm}^{-1}$ ; GC-MS analysis for (**E**)-isomer: retention time 11.40 min,  $m/z$  ( $\text{EI}^+$ ) 236 ( $\text{M}^+$ , 30), 145 (100), 115 (20), 91 (30); (**Z**)-isomer: retention time 10.62 min,  $m/z$  ( $\text{EI}^+$ ) 236 ( $\text{M}^+$ , 10), 140 (40), 115 (30), 91 (100); ( $\alpha$ )-isomer: retention time 11.20 min,  $m/z$  ( $\text{EI}^+$ ) 236 ( $\text{M}^+$ , 10), 117 (100), 115 (50), 91 (50); HRMS calc'd. for  $\text{C}_{18}\text{H}_{20}$  236.1565, found 236.1560 ( $\Delta$  -2.1 ppm).

Table 2.6.9, entry 5: **1-(4-*para*-Tolylbut-3-enyl)benzene 93e**



Using *method C*, the crude difluoro alkenylgermane (85.0 mg, 0.123 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (116.6 mg, 0.370 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (3.2 mg, 0.0123 mmol),  $\text{P}(2\text{-Tol})_3$  (5.6 mg, 0.0185 mmol), 4-bromotoluene (42.1 mg, 0.246 mmol, 25.1  $\mu\text{L}$ ) and  $\text{CuI}$  (24.5 mg, 0.123 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *styrene 93e* as a (*E*) : (*Z*) : ( $\alpha$ ) = 80 : 8 : 12 mixture of isomers (19.7 mg, 72 %) as a pale yellow oil.

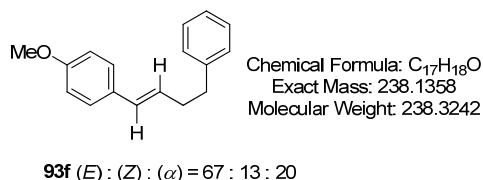
**(E)-isomer:**<sup>245</sup>  $^1\text{H}$  NMR (400 MHz):  $\delta$  2.38 (s, 3H,  $\text{CH}_3$ ), 2.55 (dt,  $J$  = 15.1, 7.0 Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 2.59 (dt,  $J$  = 15.1, 7.0 Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 2.81-2.86 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 6.26 (dt,  $J$  = 15.8, 7.0 Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 6.44 (d,  $J$  = 15.8 Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 7.12 (d,  $J$  = 7.6 Hz, 2H, ArH), 7.24-7.30 (m, 7H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ ):  $\delta$  21.1 (q), 34.9 (t), 35.9 (t), 125.9 (2d), 128.3 (3d), 128.5 (2d), 128.9 (d), 129.2 (2d), 130.2 (d), 134.9 (s), 136.6 (s), 141.8 (s); GC/MS retention time 12.35 min,  $m/z$  ( $\text{EI}^+$ ) 222 ( $\text{M}^+$ , 30), 131 (100), 115 (20), 91 (40).

**(Z)-isomer:**<sup>245</sup>  $^1\text{H}$  NMR (400 MHz):  $\delta$  2.42 (s, 3H,  $\text{CH}_3$ ), 2.67-2.77 (m, 2H,  $\text{CH}=\text{CHCH}_2$ ), 2.79-2.86 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 5.72 (dt,  $J$  = 11.5, 6.9 Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 6.46 (d,  $J$  = 11.5 Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 7.10-7.30 (m, 9H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ ):  $\delta$  21.2 (q), 30.4 (t), 37.3 (t), 126.0 (d), 128.4 (2d), 128.6 (2d), 128.7 (2d), 129.0 (2d), 129.4 (d), 131.1 (d), 134.6 (s), 136.2 (s), 141.7 (s); GC/MS retention time 11.68 min,  $m/z$  ( $\text{EI}^+$ ) 222 ( $\text{M}^+$ , 30), 129 (50), 115 (30), 91

(100).

**( $\alpha$ )-isomer:**  $^1\text{H}$  NMR (400 MHz):  $\delta$  2.39 (s, 3H, CH<sub>3</sub>), 2.54-2.61 (m, 2H, CH=CHCH<sub>2</sub>), 2.79-2.86 (m, 2H, CH<sub>2</sub>Ph), 5.08 (s, 1H, =CH), 5.33 (s, 1H, =CH), 7.10-7.30 (m, 9H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz; CDCl<sub>3</sub>):  $\delta$  19.6 (q), 34.7 (t), 36.1 (t), 111.9 (t), 126.5 (d), 126.8 (2d), 126.9 (2d), 128.5 (2d), 131.2 (2d), 136.2 (s), 137.2 (s), 142.0 (s), 147.6 (s); GC-MS retention time 11.83 min,  $m/z$  (EI<sup>+</sup>) 222 (M<sup>+</sup>, 10), 131 (100), 115 (20), 91 (20); HRMS calc'd. for C<sub>17</sub>H<sub>18</sub> 222.1409, found 222.1400 ( $\Delta$  -3.8 ppm).

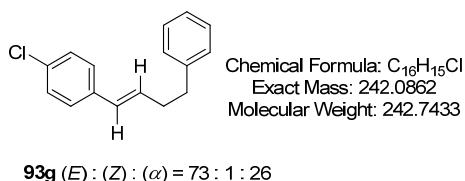
Table 2.6.9, entry 6: **1-Methoxy-4-(4-phenylbut-1-enyl)benzene 93f**



Using *method C*, the crude difluoro alkenylgermane (85.0 mg, 0.123 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (116.6 mg, 0.370 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (3.2 mg, 0.0123 mmol), P(2-Tol)<sub>3</sub> (5.6 mg, 0.0185 mmol), 4-bromoanisole (46.0 mg, 0.246 mmol, 30.8  $\mu\text{L}$ ) and CuI (24.5 mg, 0.123 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *styrene 93f* as a (*E*) : (*Z*) : ( $\alpha$ ) = 67 : 13 : 20 mixture of isomers (11.7 mg, 40 %) as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz):  $\delta$  2.53 (*E*), 2.56 (*E*) and 2.65-2.73 [(*Z*)+( $\alpha$ )] (2  $\times$  dt and m,  $J$  = 14.7, 6.9 Hz; 2H, CH=CHCH<sub>2</sub>), 2.79-2.84 [(*E*)+(*Z*)+( $\alpha$ )] (m, 2H, CH<sub>2</sub>Ph), 3.83 (*E*), 3.84 (*Z*) and 3.86 ( $\alpha$ ) (3  $\times$  s, 3H, OMe), 5.02 ( $\alpha$ ) (s, 1H, =CH), 5.27 ( $\alpha$ ) (s, 1H, =CH), 6.15 (*E*) and 6.28 (*Z*) (dt,  $J$  = 15.8, 6.9 Hz and dt,  $J$  = 12.0, 6.7 Hz; 1H, CH=CHCH<sub>2</sub>), 6.40 (*E*) and 6.44 (*Z*) (d,  $J$  = 15.8 Hz and d,  $J$  = 12.0 Hz; 1H, CH=CHCH<sub>2</sub>), 6.84-6.93 [(*E*)+(*Z*)+( $\alpha$ )] (m, 2H, ArH), 7.15-7.31 [(*E*)+(*Z*)+( $\alpha$ )] (m, 3H, ArH), 7.34-7.45 [(*E*)+(*Z*)+( $\alpha$ )] (m, 4H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz; CDCl<sub>3</sub>):  $\delta$  [(*E*)+(*Z*)+( $\alpha$ )] 30.5 (t), 34.6 (t), 34.9 (t), 35.7 (t), 37.3 (t), 55.3 (q), 55.5 (q), 113.9 (t), 122.4 (d), 124.3 (d), 126.0 (d), 126.1 (d), 126.8 (d), 128.2 (d), 128.5 (d), 128.7 (d), 128.9 (d), 129.1 (d), 129.4 (s), 130.1 (d), 131.1 (s), 134.7 (s), 134.9 (s), 136.6 (s), 141.9 (d), 142.1 (d), 142.2 (d), 158.7 (s), 159.0 (s); IR  $\nu_{\text{max}}$  (neat): 3030, 2920, 1605,

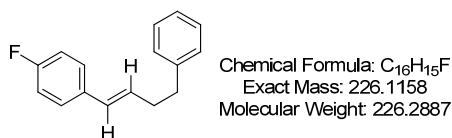
1510, 1455, 1245, 1030, 965, 855  $\text{cm}^{-1}$ ; GC/MS analysis for (*E*)-isomer: retention time 12.23 min,  $m/z$  ( $\text{EI}^+$ ) 238 ( $\text{M}^+$ , 20), 147 (100), 115 (30), 91 (40); (*Z*)-isomer: retention time 11.32 min,  $m/z$  ( $\text{EI}^+$ ) 238 ( $\text{M}^+$ , 20), 147(10), 115 (40), 91 (100); ( $\alpha$ )-isomer: retention time 11.60 min,  $m/z$  ( $\text{EI}^+$ ) 238 ( $\text{M}^+$ , 60), 147 (20), 115 (30), 104 (20), 91 (100); HRMS calc'd. for  $\text{C}_{17}\text{H}_{18}\text{O}$  238.1358, found 238.1361 ( $\Delta$  1.4 ppm).

Table 2.6.9, entry 7: **1-Chloro-4-(4-phenylbut-1-enyl)benzene 93g**



Using *method C*, the crude difluoro alkenylgermane (75.8 mg, 0.110 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (104.0 mg, 0.330 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (2.9 mg, 0.011 mmol),  $\text{P}(2\text{-Tol})_3$  (5.0 mg, 0.0165 mmol), 1-bromo-4-chlorobenzene (42.1 mg, 0.220 mmol) and  $\text{CuI}$  (21.9 mg, 0.110 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *styrene 93g* as a (*E*) : (*Z*) : ( $\alpha$ ) = 73 : 1 : 26 mixture of isomers (13.8 mg, 52 %) as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz):  $\delta$  2.54 (*E*), 2.58 (*E*) and 2.62-2.75 [(*Z*)+( $\alpha$ )] ( $2 \times \text{dt}$  and  $\text{m}$ ,  $J = 15.2, 7.1$  Hz; 2H,  $\text{CH}=\text{CHCH}_2$ ), 2.80-2.85 [(*E*)+(*Z*)+( $\alpha$ )] ( $\text{m}$ , 2H,  $\text{CH}_2\text{Ph}$ ), 5.11 ( $\alpha$ ) (s, 1H,  $=\text{CH}$ ), 5.31 ( $\alpha$ ) (s, 1H,  $=\text{CH}$ ), 5.75 (*Z*) and 6.26 (*E*) ( $2 \times \text{dt}$ ,  $J = 11.7, 7.1$  Hz and 15.8, 6.6 Hz; 1H,  $\text{CH}=\text{CHCH}_2$ ), 6.39 (*E*) and 6.43 (*Z*) ( $2 \times \text{d}$ ,  $J = 15.8$  Hz and  $J = 11.7$  Hz, 1H,  $\text{CH}=\text{CHCH}_2$ ), 7.08-7.19 [(*E*)+(*Z*)+( $\alpha$ )] ( $\text{m}$ , 2H, ArH), 7.29-7.38 ( $\text{m}$ , 7H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz;  $\text{CDCl}_3$ ): [(*E*)+(*Z*)+( $\alpha$ )]  $\delta$  34.6 (t), 34.9 (t), 35.8 (t), 37.2 (t), 113.3 (t), 126.0 (d), 127.1 (d), 127.2 (d), 127.5 (s), 128.4 (d), 128.5 (d), 128.6 (d), 129.2 (d), 129.7 (s), 130.0 (s), 130.7 (s), 136.2 (s), 137.6 (s), 141.6 (s), 146.0 (s), 146.1 (s); IR  $\nu_{\text{max}}$  (neat): 3060, 3025, 2555, 1595, 1490, 1450, 1090, 1015, 965, 836  $\text{cm}^{-1}$ ; GC/MS analysis for (*E*)-isomer: retention time 11.70 min,  $m/z$  ( $\text{EI}^+$ ) 244 [ $\text{M}^{37}\text{Cl}^+$ ], 10], 242 [ $\text{M}^{35}\text{Cl}^+$ ], 30], 151 (100), 115 (80), 91 (100); (*Z*)-isomer: retention time 11.20 min,  $m/z$  ( $\text{EI}^+$ ) 242 [ $\text{M}^{35}\text{Cl}^+$ ], 10], 151 (100), 115 (80), 91 (100); ( $\alpha$ )-isomer: retention time 11.05 min,  $m/z$  ( $\text{EI}^+$ ) 242 [ $\text{M}^{35}\text{Cl}^+$ ], 10], 115 (20), 104 (30), 91 (100); HRMS calc'd. for  $\text{C}_{16}\text{H}_{15}\text{Cl}$  242.0862, found 242.0864 ( $\Delta$  0.6 ppm).

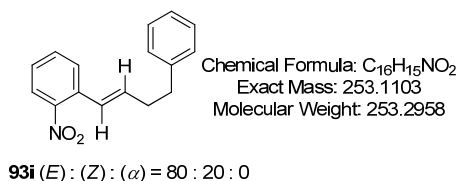
Table 2.6.9, entry 8: **1-Fluoro-4-(4-phenylbut-1-enyl)benzene 93h**



**93h** (*E*) : (*Z*) : ( $\alpha$ ) = 93 : 2 : 5

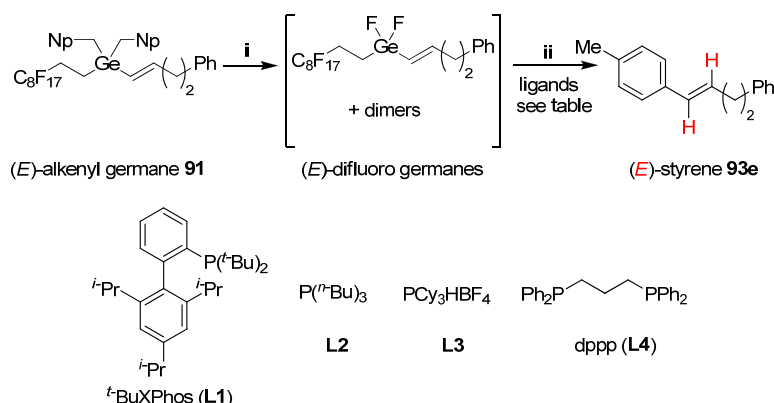
Using *method C*, the crude difluoro alkenylgermane (75.8 mg, 0.110 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (104.0 mg, 0.330 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.9 mg, 0.011 mmol), P(2-Tol)<sub>3</sub> (5.0 mg, 0.0165 mmol), 1-chloro-4-fluorobenzene (28.7 mg, 0.220 mmol, 23.4  $\mu$ L) and CuI (21.9 mg, 0.110 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *styrene 93h* as a (*E*) : (*Z*) : ( $\alpha$ ) = 93 : 2 : 5 mixture of isomers (14.4 mg, 58 %) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz):  $\delta$  2.54 (*E*), 2.57 (*E*) and 2.60-2.71 [(*Z*)+( $\alpha$ )] (2  $\times$  dt and m, *J* = 15.0, 7.1 Hz and *J* = 15.0, 7.1 Hz; 2H, CH=CHCH<sub>2</sub>), 2.76-2.84 [(*E*)+(*Z*)+( $\alpha$ )] (m, 2H, CH<sub>2</sub>Ph), 5.08 ( $\alpha$ ) (s, 1H, =CH), 5.27 ( $\alpha$ ) (s, 1H, =CH), 5.72 (*Z*) and 6.20 (*E*) (2  $\times$  dt, *J* = 11.6, 7.1 Hz and *J* = 15.7, 6.8 Hz; 1H, CH=CHCH<sub>2</sub>), 6.41 (*E*) and 6.43 (*Z*) (2  $\times$  d, *J* = 15.7, 6.8 Hz and *J* = 11.6, 7.1 Hz; 1H, CH=CHCH<sub>2</sub>), 6.98-7.04 [(*E*)+(*Z*)+( $\alpha$ )] (m, 2H, ArH), 7.20-7.36 [(*E*)+(*Z*)+( $\alpha$ )] (m, 7H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>):  $\delta$  31.1 (t) 34.8 (t), 34.9 (t), 35.6 (t), 36.0 (t), 115.6 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.5 Hz), 118.2 (s), 121.4 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz), 124.3 (d), 126.8 (d), 128.2 (d), 128.6 (d), 128.7 (d), 129.4 (s), 131.1 (s), 145.3 (d, <sup>1</sup>*J*<sub>C-F</sub> = 110.2 Hz); The <sup>13</sup>C NMR signals for the (*Z*)- and ( $\alpha$ )-isomer were unable to be identified due to the low abundance of these isomers. <sup>19</sup>F NMR (376MHz; CDCl<sub>3</sub>):  $\delta$  -115.5 (s, 1F); IR  $\nu_{\max}$  (neat): 3060, 3025, 2965, 1600, 1510, 1455, 1230, 1155, 965, 850 cm<sup>-1</sup>; GC/MS analysis for (***E***)-isomer: retention time 10.43 min, *m/z* (EI<sup>+</sup>) 226 (M<sup>+</sup>, 30), 135 (100), 115 (40), 91 (40); (***Z***)-isomer: retention time 9.95 min, *m/z* (EI<sup>+</sup>) 226 (M<sup>+</sup>, 10), 135 (100), 115 (30), 91 (50); ( $\alpha$ )-isomer: retention time 9.78 min, *m/z* (EI<sup>+</sup>) 226 (M<sup>+</sup>, 10), 130 (10), 104 (20), 91 (100); HRMS calc'd. for C<sub>16</sub>H<sub>15</sub>F 226.1158, found 226.1157 ( $\Delta$  -0.3 ppm).

Table 2.6.9, entry 9: **1-(4-(2-Nitrophenyl)but-3-enyl)benzene 93i**



Using *method C*, the crude difluoro alkenylgermane (75.8 mg, 0.110 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of  $Cu(BF_4)_2 \cdot nH_2O$ , TBAF (104.0 mg, 0.330 mmol),  $PdCl_2(MeCN)_2$  (2.9 mg, 0.011 mmol),  $P(2-Tol)_3$  (5.0 mg, 0.0165 mmol), 1-bromo-2-nitrobenzene (44.4 mg, 0.220 mmol, 23.4  $\mu$ L) and CuI (21.9 mg, 0.110 mmol) were employed. Purification by FC (hexane/EtOAc, 97/3) gave *styrene 93i* as a (*E*) : (*Z*) : ( $\alpha$ ) = 80 : 20 : 0 mixture of isomers (13.3 mg, 48 %) as a pale yellow oil.  $^1H$  NMR (400 MHz):  $\delta$  2.41 (*E*), 2.45 (*E*) and 2.61-2.70 (*Z*) ( $2 \times$  dt and m,  $J = 14.1, 7.5$  Hz; 2H,  $CH=CHCH_2$ ), 2.73 (*Z*) and 2.86 (*E*) ( $2 \times$  t,  $J = 7.0$  Hz and 7.6 Hz; 2H,  $CH_2Ph$ ), 5.89 (*Z*) and 6.27 (*E*) ( $2 \times$  dt,  $J = 11.6, 7.4$  Hz and  $J = 15.6, 6.8$  Hz; 1H,  $CH=CHCH_2$ ), 6.76 (*Z*) and 6.91 (*E*) ( $2 \times$  d,  $J = 11.6$  Hz and  $J = 15.6$  Hz, 1H,  $CH=CHCH_2$ ), 7.23-7.35 [(*E*)+(*Z*)] (m, 3H, ArH), 7.40-7.52 [(*E*)+(*Z*)] (m, 4H, ArH), 7.86 (*E*) and 7.90 (*Z*) ( $2 \times$  d,  $J = 7.6$  Hz and  $J = 7.9$  Hz; 1H, ArH), 8.05 (*E*) and 8.25 (*Z*) ( $2 \times$  t,  $J = 7.6$  Hz and  $J = 7.9$  Hz; 1H, ArH);  $^{13}C$  NMR (100.7 MHz;  $CDCl_3$ ): [(*E*)+(*Z*)]  $\delta$  35.1 (t), 35.9 (t), 36.9 (t), 37.4 (t), 124.3 (d), 128.6 (d), 128.7 (d), 128.9 (d), 129.5 (d), 131.8 (d), 132.5 (d), 134.4 (s), 135.2 (s), 135.9 (s), 149.1 (s), 149.2 (s); IR  $\nu_{max}$  3060, 2925, 1604, 1520, 1348, 1099, 963, 835  $cm^{-1}$ ; GC/MS analysis for (***E***)-isomer: retention time 12.60 min,  $m/z$  ( $EI^+$ ) 253 ( $M^+$ , 40), 207 (30), 162 (70), 91 (100); (***Z***)-isomer: retention time 11.95 min,  $m/z$  ( $EI^+$ ) 253 ( $M^+$ , 20), 207 (30), 162 (60), 91 (100); HRMS calc'd. for  $C_{16}H_{15}NO_2$  253.1103, found 253.1108 (D 2.0 ppm).

Screening for supporting ligands to effect stereoselective formation of (*E*)-styrene **93e** (Table 2.6.10)



Using a modification of *method C* in which *t*-BuXPhos (**L1**),  $\text{P}(\text{n-Bu})_3$  (**L2**),  $\text{PCy}_3\text{HBF}_4$  (**L3**) (Hunig's base (15 mol%) was also employed in this occasion) and dppp (**L4**) were used to replace of P(2-Tol). The crude difluoro alkenylgermane (86.2 mg, 0.125 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (118.1 mg, 0.375 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (3.2 mg, 0.0125 mmol), 4-bromotoluene (42.8 mg, 0.250 mmol, 30.8  $\mu\text{L}$ ) and CuI (24.9 mg, 0.125 mmol) were employed. Purification by FC (hexane/EtOAc, 90/10) gave (*E*)-styrene **93e** as a major or exclusive isomer.

Using  $\text{PCy}_3\text{HBF}_4$  (**L3**) as supporting ligand (Scheme 2.6.43)

Using modified *method C*, the crude difluoro alkenylgermane (86.2 mg, 0.125 mmol) from the photolysis of alkenylgermane **91** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (118.1 mg, 0.375 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (3.2 mg, 0.0125 mmol),  $\text{PCy}_3\text{-HBF}_4$  (6.9 mg, 0.0188 mmol), Hunig's base (2.4 mg, 0.0188 mmol, 3.3  $\mu\text{L}$ ) 4-bromoacetophenone (49.9 mg, 0.250 mmol) and CuI (24.9 mg, 0.125 mmol) were employed. Purification by FC (hexane/EtOAc, 90/10) gave styrene **93c** (12.5 mg, 40 %) as a pale yellow solid. Analytical data as shown above.

Cross-coupling of styrenyl germane **92** with aryl bromides (Table 2.6.11)

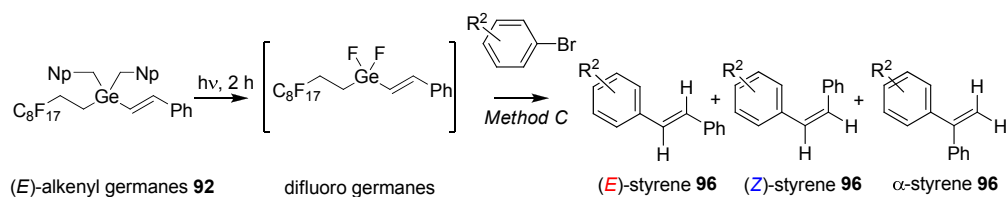
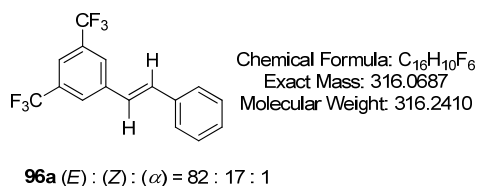
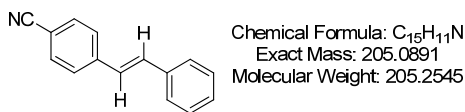


Table 2.6.11, entry 1: **3,5-Bis(trifluoromethyl)stilbene 96a**<sup>246</sup>



Using *method C*, the crude difluoro alkenylgermane (65.5 mg, 0.099 mmol) from the photolysis of alkenylgermane **92** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (93.7 mg, 0.297 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.6 mg, 0.0099 mmol), P(2-Tol)<sub>3</sub> (4.5 mg, 0.0149 mmol), 3,5-bis-(trifluoromethyl)bromobenzene (58.0 mg, 0.198 mmol, 34.1  $\mu$ L) and CuI (19.7 mg, 0.099 mmol) were employed. Purification by FC (hexane/EtOAc, 95/5) gave *styrene 96a* as a (*E*) : (*Z*) : ( $\alpha$ ) = 82 : 17 : 1 mixture of isomers (18.2 mg, 58 %) as a white solid. mp. 78-80 °C; <sup>1</sup>H NMR (400 MHz):  $\delta$  5.56 ( $\alpha$ ) (s, 1H, =CH), 5.69 ( $\alpha$ ) (s, 1H, =CH), 6.63 (*Z*) and 7.17 (*E*) (2  $\times$  d, J = 12.1 Hz and 16.3 Hz; 1H, =CH), 6.87 (*Z*) and 7.28 (*E*) (2  $\times$  d, J = 12.1 Hz and 16.3 Hz; 1H, =CH), 7.30-7.39 [(*E*)+(*Z*)+( $\alpha$ )] (m, 3H, ArH), 7.41-7.45 [(*E*)+(*Z*)+( $\alpha$ )] (m, 2H, ArH), 7.96 [(*Z*)+( $\alpha$ )] and 7.97 (*E*) (s, 1H, ArH), 8.34 [(*Z*)+( $\alpha$ )] and 8.36 (*E*) (s, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>): [(*E*)+(*Z*)+( $\alpha$ )]  $\delta$  120.8 (d), 123,4 (2s, <sup>1</sup>J<sub>C-F</sub> = 272.9 Hz, 2  $\times$  CF<sub>3</sub>), 125.5 (d), 126.2 (d), 126.9 (d), 127.4 (d), 128.3 (d), 128.8 (d), 128.9 (d), 132.0 (2s, <sup>2</sup>J<sub>C-F</sub> = 32.8 Hz), 132.5 (d), 136.0 (s), 139.4 (s), 140.4 (s); <sup>19</sup>F NMR (376MHz; CDCl<sub>3</sub>):  $\delta$  -115.2 (s, 6F, 2  $\times$  CF<sub>3</sub>); IR  $\nu_{\text{max}}$  (neat): 3040, 1790, 1640, 1615, 1495, 1380, 1280, 1170, 1130, 1110, 960, 895 cm<sup>-1</sup>; GC/MS analysis for (***E***)-isomer: retention time 9.02 min, *m/z* (EI<sup>+</sup>) 316 (M<sup>+</sup>, 100), 301 (30), 245 (520), 227 (20), 178 (60); (***Z***)-isomer: retention time 7.57 min, *m/z* (EI<sup>+</sup>) 316 (M<sup>+</sup>, 100), 301 (30), 245 (50), 226 (30), 178 (50); ( $\alpha$ )-isomer: retention time 7.42 min, *m/z* (EI<sup>+</sup>) 316 (M<sup>+</sup>, 100), 247 (20), 227 (20), 178 (40); HRMS calc'd. for C<sub>16</sub>H<sub>10</sub>F<sub>6</sub> 316.0687, found 316.0684 ( $\Delta$  -0.9 ppm).

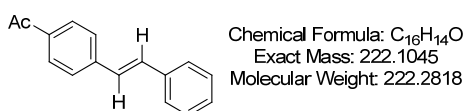
Table 2.6.11, entry 2: **4-Cyanostilbene 96b**<sup>247</sup>



**96b** (*E*)- : (*Z*)- : ( $\alpha$ )- = 90 : 10 : 0

Using *method C*, the crude difluoro alkenylgermane (65.5 mg, 0.099 mmol) from the photolysis of alkenylgermane **92** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (93.7 mg, 0.297 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.6 mg, 0.0099 mmol), P(2-Tol)<sub>3</sub> (4.5 mg, 0.0149 mmol), 4-cyanobromobenzene (36.0 mg, 0.198 mmol) and CuI (19.7 mg, 0.099 mmol) were employed. Purification by FC (hexane/EtOAc, 90/10) gave *styrene 96b* as a (*E*) : (*Z*) : ( $\alpha$ ) = 90 : 10 : 0 mixture of isomers (12.2 mg, 60 %) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz):  $\delta$  7.02 (*Z*) and 7.13 (*E*) (d, *J* = 11.2 Hz and 16.4 Hz; 1H, =CH), 7.09 (*Z*) and 7.25 (*E*) (d, *J* = 11.2 Hz and 16.4 Hz; 1H, =CH), 7.27-7.32 [(*E*)+(*Z*)] (m, 1H, ArH), 7.37 (*E*) and 7.40 (*Z*) (2  $\times$  t, *J* = 7.4 Hz and 7.4 Hz; 2H, ArH), 7.43-7.55 [(*E*)+(*Z*)] (m, 6H, ArH); GC/MS analysis for (***E***)-isomer: retention time 11.95 min, *m/z* (EI<sup>+</sup>) 204 (M<sup>+</sup>, 100), 190 (50), 101 (30), 89 (30); (***Z***)-isomer: retention time 10.72 min, *m/z* (EI<sup>+</sup>) 204 (M<sup>+</sup>, 100), 190 (30), 100 (40), 87 (30).

Table 2.6.11, entry 3: **4-Acetylstilbene 96c**<sup>248</sup>

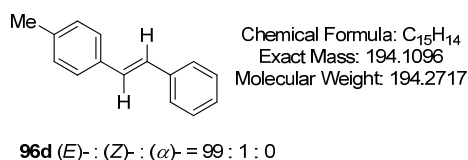


**96c** (*E*)- : (*Z*)- : ( $\alpha$ )- = 100 : 0 : 0

Using *method C*, the crude difluoro alkenylgermane (65.5 mg, 0.099 mmol) from the photolysis of alkenylgermane **92** for 2 h with 8 equivalents of Cu(BF<sub>4</sub>)<sub>2</sub>·nH<sub>2</sub>O, TBAF (93.7 mg, 0.297 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (2.6 mg, 0.0099 mmol), P(2-Tol)<sub>3</sub> (4.5 mg, 0.0149 mmol), 4-bromoacetophenone (39.4 mg, 0.198 mmol) and CuI (19.7 mg, 0.099 mmol) were employed. Purification by FC (hexane/EtOAc, 90/10) gave *styrene 96c* as a single isomer (12.2 mg, 60 %) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz):  $\delta$  2.64 (s, 3H, CH<sub>3</sub>), 7.16 (d, *J* = 16.3 Hz, 1H, =CH), 7.27 (d, *J* = 16.3 Hz, 1H, =CH), 7.30-7.33 (m, 1H, ArH), 7.42 (d, *J* = 7.6 Hz, 2H, ArH), 7.58 (d, *J* = 7.6 Hz,

2H, ArH), 7.62 (d,  $J = 8.3$  Hz, 2H, ArH), 7.99 (d,  $J = 8.3$  Hz, 2H, ArH);  $m/z$  ( $\text{EI}^+$ ) 222 ( $\text{M}^+$ , 80), 207 (100), 178 (70), 152 (40), 104 (20); HRMS calc'd. for  $\text{C}_{16}\text{H}_{14}\text{O}$  222.1045, found 222.1044 ( $\Delta$  -0.3 ppm).

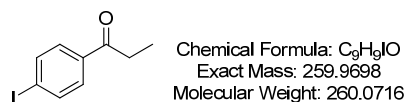
Table 2.6.11, entry 4: **4-Methylstilbene 96d**<sup>247</sup>



Using *method C*, the crude difluoro alkenylgermane (65.5 mg, 0.099 mmol) from the photolysis of alkenylgermane **92** for 2 h with 8 equivalents of  $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$ , TBAF (93.7 mg, 0.297 mmol),  $\text{PdCl}_2(\text{MeCN})_2$  (2.6 mg, 0.0099 mmol),  $\text{P}(2\text{-Tol})_3$  (4.5 mg, 0.0149 mmol), 4-bromotoluene (33.9 mg, 0.198 mmol) and  $\text{CuI}$  (19.7 mg, 0.099 mmol) were employed. Purification by FC (hexane/EtOAc, 90/10) gave *styrene 96d* as a ( $E$ ) : ( $Z$ ) : ( $\alpha$ ) = 99 : 1 : 0 mixture of isomers (12.2 mg, 60 %) as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz):  $\delta$  2.39 (s, 3H,  $\text{CH}_3$ ), 7.08 (d,  $J = 16.4$  Hz, 1H,  $=\text{CH}$ ), 7.13 (d,  $J = 16.4$  Hz, 1H,  $=\text{CH}$ ), 7.20 (d,  $J = 8.0$  Hz, 2H, ArH), 7.27-7.30 (m, 1H, ArH), 7.38 (t,  $J = 7.6$  Hz, 2H, ArH), 7.45 (t,  $J = 8.0$  Hz, 2H, ArH), 7.53 (t,  $J = 7.6$  Hz, 2H, ArH); The ( $Z$ )-isomer was not detected by  $^1\text{H}$  NMR. GC/MS analysis for (***E***)-isomer: retention time 10.48 min,  $m/z$  ( $\text{EI}^+$ ) 194 ( $\text{M}^+$ , 80), 179 (100), 115 (40), 89 (30); (***Z***)-isomer: retention time 10.25 min,  $m/z$  ( $\text{EI}^+$ ) 194 ( $\text{M}^+$ , 100), 179 (90), 115 (30), 89 (20); HRMS calc'd. for  $\text{C}_{15}\text{H}_{14}$  194.1096, found 194.1096 ( $\Delta$  0 ppm).

### 4.3 Development of efficient *ipso*-iododegermylation as a method for radio-labelling

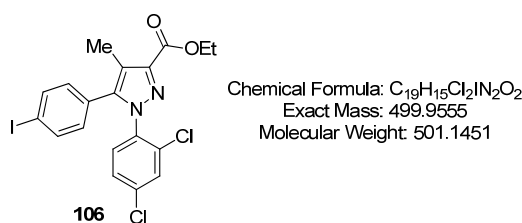
#### 4-Iodopropiophenone<sup>249</sup>



4-Bromopropiophenone (5.0 g, 23.47 mmol), copper(I) iodide (234.0 mg, 1.17 mmol) and sodium iodide (7.04 g, 47.0 mmol) were suspended in 1,4-dioxane (20 mL).

*N,N*-Dimethylethylenediamine (200 mg, 2.35 mmol, 244  $\mu$ L) was added to the reaction vessel and the contents heated to reflux for sixteen hours. After cooling, the resultant solution was diluted with saturated aqueous ammonia (50 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 50$  mL). The organic layers were dried over sodium sulfate and concentrated *in vacuo* to give 4-iodopropiophenone as white needles (5.96 g, 97 %). mp 56-58  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.21 (t,  $J = 7.2$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.96 (q,  $J = 7.2$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 7.67 (d,  $J = 8.4$  Hz, 2H, ArH), 7.82 (d,  $J = 8.4$  Hz, 2H, ArH); IR (nujol $^\text{®}$ ): 1271, 1389, 1576, 1675, 2968  $\text{cm}^{-1}$ ;  $m/z$  ( $\text{EI}^+$ ): 260 ( $\text{M}^+$ ). HRMS calc'd. for  $\text{C}_9\text{H}_9\text{IO}$  259.9698, found 259.9689 ( $\Delta$  -3.4 ppm).

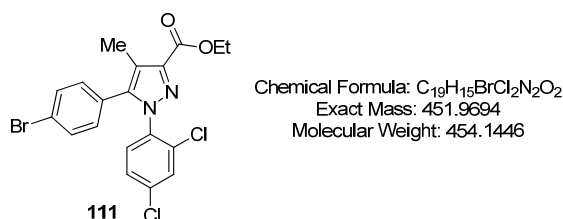
**1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid ethyl ester 106**



A solution of lithium hexamethyldisilazide (LHMDS) (16.6 mL, 1.0 M in hexanes, 16.6 mmol) was placed into a two-necked flask fitted with a pressure-equalised dropping funnel and cooled to  $0^\circ\text{C}$ . 4-Iodopropiophenone (3.47 g, 13.3 mmol) was dissolved in methylcyclohexane (10 mL) and used to charge the dropping funnel, before being slowly added to the lithium hexamethyldisilazide over a period of 20 min. The resultant solution was left to stir for 1 h before dropwise addition of a solution of diethyl oxalate (2.43 g, 16.6 mmol, 2.25 mL) in methylcyclohexane (5 mL). A yellow suspension formed which was allowed to stir for 16 h. The yellow solid product deposited after this period was collected by filtration and washed extensively with cold ether to give an orange solid (3.6 g). A portion (2.9 g) of this solid was added over a period of 2 h to a solution of 2,4-dichlorophenyl hydrazine hydrochloride (1.67 g, 7.8 mmol) in 95 % ethanol (40 mL). 500  $\mu\text{L}$  conc. hydrochloric was also added to the reaction mixture as a catalyst. The mixture was then allowed to stir for 16 h. The reaction broth was subsequently concentrated and re-dissolved in 20 mL of glacial acetic acid before heating to reflux for 16 h. After

this time the reaction was cooled and excess acetic acid removed under vacuum. The resultant crude product was dissolved in EtOAc and washed with water (20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate and the solvent evaporated to give an orange solid. Purification by FC (hexane/EtOAc, 90/10) to yield *pyrazole ethyl ester 106* as an orange solid (3.35 g, 85 %). mp. 153-155 °C. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): δ 1.42 (t, *J* = 7.1 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.33 (s, 3H, CH<sub>3</sub>), 4.45 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 6.86 (d, *J* = 8.3, 2H, ArH), 7.20-7.46 (m, 3H, ArH), 7.66 (d, *J* = 8.3, 2H, ArH). <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>): δ 9.6 (q), 14.3 (q), 60.8 (t), 95.0 (s), 119.0 (s), 123.1 (s), 127.7 (d), 128.0 (s), 130.0 (d), 131.1 (2d), 131.7 (2d), 132.9 (s), 135.8 (s), 135.9 (s), 137.7 (d), 142.9 (s), 162.7 (s). IR ν<sub>max</sub> (neat): 3010, 2915, 1710, 1490, 1430, 1385, 1360, 1300, 1250, 1190, 1100, 1020, 1000, 965, 870, 650 cm<sup>-1</sup>; MS (ESI<sup>+</sup>): 501 (MH<sup>+</sup>), 523 (MNa<sup>+</sup>). HRMS calculated for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>I (MH<sup>+</sup>) 500.9643, found 500.9612 (Δ 4.2 ppm).

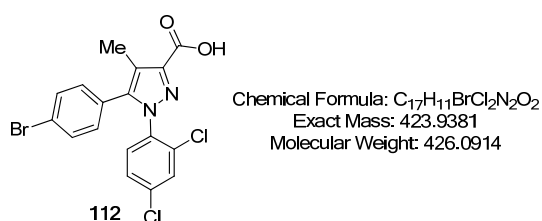
**1-(2,4-Dichlorophenyl)-5-(4-bromophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid ethyl ester **111****<sup>250</sup>



The bromo pyrazole ethyl ester **111** was prepared by the same procedure described for the corresponding iodide above. Thus, 4-bromopropiophenone (4.5 g, 21.1 mmol), a solution of LHMDs (26.4 mL, 26.4 mmol, 1 M in hexanes), diethyl oxalate (3.85 g, 26.4 mmol, 3.58 mL) and 2,4-dichlorophenyl hydrazine hydrochloride (4.96 g, 23.2 mmol) were used. Purification by FC (hexane/EtOAc, 90/10) gave *pyrazole ethyl ester 111* (8.44 g, 88 %) as an orange solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.40 (t, *J* = 7.2 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.31 (s, 3H, CH<sub>3</sub>), 4.43 (q, *J* = 7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 6.99 (d, *J* = 8.4 Hz, 2H, ArH), 7.27 (dd, *J* = 8.5, 2.0 Hz, 1H, ArH), 7.33 (d, *J* = 8.5 Hz, 1H, ArH), 7.36 (d, *J* = 2.0 Hz, 1H, ArH), 7.44 (d, *J* = 8.4 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz, CDCl<sub>3</sub>): δ 9.6 (q), 14.4 (q), 60.9 (t), 119.1 (s), 123.2 (s), 127.4 (s), 127.7 (d), 130.0 (d), 130.6 (d), 131.1 (2d), 131.7 (2d), 132.9 (s), 135.8 (s), 136.0 (s),

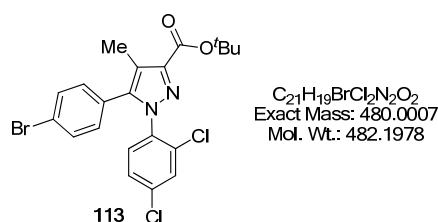
142.8 (s), 142.9 (s), 162.6 (s); IR  $\nu_{\text{max}}$  (neat): 3025, 2920, 1715, 1490, 1430, 1385, 1365, 1300, 1240, 1190, 1100, 1020, 980, 965, 880,  $\text{cm}^{-1}$ ; MS ( $\text{Cl}^+$ ) 455 ( $\text{MH}^+$ , 100); HRMS ( $\text{Cl}^+$ ) calc'd. for  $\text{C}_{19}\text{H}_{16}\text{BrCl}_2\text{N}_2\text{O}_2$  452.9772 [ $\text{M}(^{79}\text{Br})\text{H}^+$ ], found 452.9780 ( $\Delta$  1.7 ppm).

**5-(4-Bromophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid **112****<sup>251</sup>



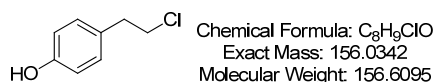
To a solution of *pyrazole ethyl ester* **111** (1.02 g, 2.246 mmol) in THF (15 mL) was added NaOH (2g, 50 mmol) and  $\text{H}_2\text{O}$  (4 mL). The reaction mixture was refluxed at 70 °C for 6 h and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo*. The residue was purified by recrystallisation to give *pyrazole carboxylic acid* **112** as a white solid (0.947 g, 99 %);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.35 (s, 3H,  $\text{CH}_3$ ), 7.01 (d,  $J = 8.4$  Hz, 2H, ArH), 7.30 (dd,  $J = 8.5, 2.0$  Hz, 1H, ArH), 7.34 (d,  $J = 8.5$  Hz, 1H, ArH), 7.41 (d,  $J = 2.0$  Hz, 1H, ArH), 7.47 (d,  $J = 8.4$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (100.7 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.6 (q), 119.6 (s), 123.5 (s), 127.2 (s), 127.9 (d), 130.2 (d), 130.5 (d), 131.1 (2d), 131.9 (2d), 132.8 (s), 135.6 (s), 136.3 (s), 142.1 (s), 143.4 (s), 166.0 (s);  $m/z$  ( $\text{Cl}^+$ ) (rel. intensity) 452 [ $\text{M}(^{79}\text{Br})\text{H}^+$ , 100], 339 (60), 297 (20); HRMS ( $\text{Cl}^+$ ) calc'd for  $\text{C}_{17}\text{H}_{12}^{79}\text{Br}^{35}\text{Cl}_2\text{N}_2\text{O}_2$  ( $\text{MH}^+$ ) 424.9459, found 424.9447 ( $\Delta$  -2.9 ppm).

**5-(4-Bromophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid *tert*-butyl ester **113****



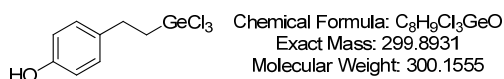
According to the method of Armstrong,<sup>252</sup> to a solution of pyrazole carboxylic acid **112** (0.947 g, 2.223 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added *tert*-butyl 2,2,2-trichloroacetimidate (TBTA, 1.215 g, 5.56 mmol) in cyclohexane (10 mL) and BF<sub>3</sub>-Et<sub>2</sub>O (27.3  $\mu$ L, 0.223 mmol) for 16 h at rt. The resulting mixture was extracted with Et<sub>2</sub>O (3  $\times$  50 mL) and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo*. The residue was purified by FC (Hexane/EtOAc, 10/90) to give *pyrazole carboxylic acid tert-butyl ester* **113** as a colourless oil (0.911 g, 85 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.63 (s, 9H, 3  $\times$  CH<sub>3</sub>), 2.28 (s, 3H, CH<sub>3</sub>), 6.98 (d, *J* = 8.4 Hz, 2H, ArH), 7.29 (dd, *J* = 8.5, 2.0 Hz, 1H, ArH), 7.35 (d, *J* = 8.5 Hz, 1H, ArH), 7.36 (d, *J* = 2.0 Hz, 1H, ArH), 7.44 (d, *J* = 8.4 Hz, 2H, ArH); <sup>13</sup>C (100.7 MHz, CDCl<sub>3</sub>):  $\delta$  10.0 (q), 20.3 (3q), 81.8 (s), 118.3 (s), 123.1 (s), 127.3 (s), 127.7 (d), 130.1 (d), 130.7 (d), 131.1 (2d), 131.8 (2d), 132.9 (s), 135.8 (s), 136.0 (s), 142.7 (s), 144.5 (s), 162.0 (s); IR  $\nu_{\text{max}}$  (neat): 3010, 2915, 1710, 1490, 1430, 1385, 1360, 1300, 1250, 1190, 1135, 1100, 1055, 1020, 965, 870 cm<sup>-1</sup>; *m/z* (CI<sup>+</sup>) (rel. intensity) 481 [M(<sup>79</sup>Br)H<sup>+</sup>, 80], 427 (55), 367 (50), 311 (30); HRMS (CI<sup>+</sup>) calc'd for C<sub>21</sub>H<sub>20</sub><sup>79</sup>Br<sup>35</sup>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> (MH)<sup>+</sup> 481.0085, found 481.0089 ( $\Delta$  0.8 ppm).

#### 4-(2-Chloroethyl)phenol<sup>252</sup>



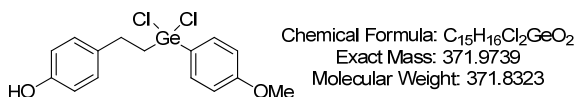
According to the method of Ehrlich,<sup>252</sup> 4-(2-hydroxyethyl)phenol (8 g, 58 mmol) and conc. HCl (60 mL) were heated in a Carius tube at 100 °C for three hours. After cooling, the reaction mixture was poured into water (150 mL) and extracted with ether (100 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo* to give a brown oil. Purification by FC (CH<sub>2</sub>Cl<sub>2</sub>) gave 4-(2-chloroethyl)phenol as a pale brown oil (8.63 g, 98 %). <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta$  2.98 (t, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 3.67 (t, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Cl), 4.89 (br s, 1H, OH), 6.78 (d, *J* = 8.4 Hz, 2H, ArH), 7.09 (d, *J* = 8.4 Hz, 2H, ArH).

#### 4-(2-Trichlorogermylethyl)phenol<sup>138</sup>



According to the method of Turner,<sup>138</sup> 4-(2-chloroethyl)phenol (7.1 g, 45.3 mmol), and dichlorogermylene 1,4-dioxane complex **1** (10.5 g, 45.3 mmol) were heated together in a Carius tube at 150 °C for 16 h. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and added dropwise to water (100 mL). The resulting white precipitate was collected by filtration, washed with water (3 × 100 mL) then CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL) and dried under suction. The dried precipitate was dissolved in conc. hydrochloric acid (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give 4-(2-trichlorogermylethyl)phenol as a colourless oil (12.50 g, 92 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.27-2.33 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>GeCl<sub>3</sub>), 2.95-3.00 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>GeCl<sub>3</sub>), 4.75 (br s, 1H, OH), 6.79 (d, *J* = 8.5 Hz, 2H, ArH), 7.10 (d, *J* = 8.5 Hz, 2H, ArH).

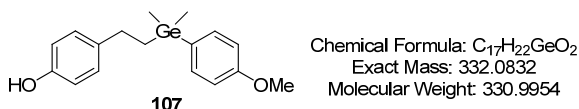
#### 4-{2-[(4-Methoxyphenyl)dichlorogermyl]ethyl}phenol<sup>138</sup>



To a solution of 4-(2-trichlorogermylethyl)phenol (6.0 g, 20.0 mmol) in THF (50.0 mL) was added a solution of *para*-methoxyphenylmagnesiumbromide (200 mL, 100.0 mmol, 0.5 M in THF). The resulting reaction mixture was stirred at reflux for 3 h. The yellow reaction mixture was cooled to 0 °C before quenching dropwise with methanol until effervescence ceased. The reaction mixture was diluted with Et<sub>2</sub>O (20.0 mL) and washed with water (2 × 20.0 mL). The combined organic extracts were dried over sodium sulfate and the solvent was removed *in vacuo* to give *tris-para*-anisylgermyl phenol as a colourless oil. The *tris-para*-anisylgermyl phenol was then suspended in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and conc. HCl (50.0 mL) added. The reaction mixture was stirred for 16 h and the solvent was then removed *in vacuo* to give 4-{2-[(4-methoxyphenyl)dichlorogermyl]ethyl}phenol as a brown oil (7.42 g, 99 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.03-2.10 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>Ge), 2.80-2.89 (m, 2H,

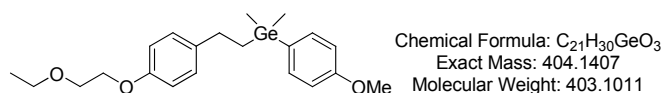
ArCH<sub>2</sub>CH<sub>2</sub>Ge), 3.84 (s, 3H, OCH<sub>3</sub>), 4.82 (br s, 1H, OH), 6.73 (d, *J* = 8.4 Hz, 2H, ArH), 6.97 (d, *J* = 8.7 Hz, 2H, ArH), 7.07 (d, *J* = 8.4 Hz, 2H, ArH), 7.48 (d, *J* = 8.7 Hz, 2H, ArH). <sup>13</sup>C NMR (100.7 MHz, CDCl<sub>3</sub>): δ 27.8 (t), 28.6 (t), 55.4 (q), 114.6 (2d), 115.5 (2d), 126.7 (s), 129.4 (2d), 133.8 (2d+s), 154.1 (s), 162.1 (s).

#### 4-{2-[(4-Methoxyphenyl)dimethylgermyl]ethyl}phenol **107**<sup>138</sup>



To a solution of 4-{2-[(4-methoxyphenyl)dichlorogermylethyl]phenol (5.0 g, 13.45 mmol) in THF (50 mL) was cooled to -40 °C and added a solution of MeLi (25.2 mL, 40.34 mmol, 1.6 M in Et<sub>2</sub>O). The solution was allowed to warm up to RT for 16 h before quenching with the cautious addition of sat. NH<sub>4</sub>Cl solution. The crude product was extracted from the resulting biphasic mixture with Et<sub>2</sub>O (3 × 200 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification by FC (hexane/EtOAc, 50/50) gave *dimethylgermyl phenol 107* as a yellow oil (3.83 g, 86 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.34 (s, 6H, 2 × CH<sub>3</sub>), 1.20-1.27 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>Ge), 2.59-2.67 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>Ge), 3.82 (s, 3H, OCH<sub>3</sub>), 4.64 (br s, 1H, OH), 6.73 (d, *J* = 8.5 Hz, 2H, ArH), 6.92 (d, *J* = 8.5 Hz, 2H, ArH), 7.04 (d, *J* = 8.5 Hz, 2H, ArH), 7.38 (d, *J* = 8.5 Hz, 2H, ArH); <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>): δ -3.6 (2q), 18.1 (t), 30.1 (t), 55.1 (q), 113.8 (2d), 115.1 (2d), 128.9 (2d), 132.1 (s), 134.4 (2d), 136.9 (s), 153.4 (s), 159.8 (s); *m/z* (EI<sup>+</sup>) 332 (M<sup>+</sup>, 5), 317 (20), 224 (50), 211 (100), 197 (50), 121 (30), 84 (70); HRMS calc'd. for C<sub>17</sub>H<sub>22</sub><sup>74</sup>GeO<sub>2</sub> 332.0832, found 332.0831 (Δ -0.2 ppm).

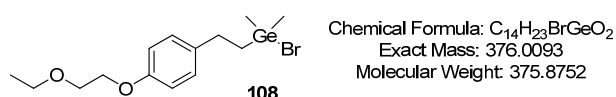
#### 4-[2-Dimethyl(4-methoxyphenyl)germylethyl]phenyl ethoxyethyl ether<sup>138</sup>



To a solution of dimethylgermyl phenol **107** (1.52 g, 4.59 mmol) in DMF (10 mL) was added K<sub>2</sub>CO<sub>3</sub> (3.17 g, 23.0 mmol), tributylammonium iodide (TBAI) (169.4 mg, 0.46mmol) and 2-chlorodiethylether (4.98 g, 46.0 mmol, 5.04 mL). The reaction

mixture was warmed to 80 °C for 24 h, diluted with Et<sub>2</sub>O (20.0 mL), and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred. Following extraction with Et<sub>2</sub>O (2 × 20.0 mL), the combined organic extracts were dried over sodium sulfate and evaporated *in vacuo* to give yellow oily residue which was purified by FC (hexane/EtOAc, 90/10) to give pure 4-[2-Dimethyl(4-methoxyphenyl)germylethyl]phenyl ethoxyethyl ether as a pale yellow oil (1.46 g, 79 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.34 (s, 6H, 2 × CH<sub>3</sub>), 1.20-1.28 (m, 5H, ArCH<sub>2</sub>CH<sub>2</sub>Ge + OCH<sub>2</sub>CH<sub>3</sub>), 2.60-2.66 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>Ge), 3.60 (q, *J* = 7.0 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 3.78 (t, *J* = 5.0 Hz, OCH<sub>2</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 4.01 (t, *J* = 5.0 Hz, OCH<sub>2</sub>), 6.83 (d, *J* = 8.6 Hz, 2H, ArH), 6.92 (d, *J* = 8.4 Hz, 2H, ArH), 7.07 (d, *J* = 8.6 Hz, 2H, ArH), 7.38 (d, *J* = 8.4 Hz, 2H, ArH), <sup>13</sup>C NMR (100.7 MHz; CDCl<sub>3</sub>): δ -3.5 (q), 15.2 (q), 18.2 (t), 30.2 (t), 55.1 (q), 66.9 (t), 67.5 (t), 69.1 (t), 113.8 (2d), 114.6 (2d), 128.7 (2d), 132.0 (s), 134.5 (2d), 137.1 (s), 156.9 (s), 159.9 (s); *m/z* (EI<sup>+</sup>) 403 (M<sup>+</sup>, 20), 388 (30), 211 (100), 193 (40); HRMS calcd for C<sub>21</sub>H<sub>30</sub><sup>74</sup>GeO<sub>3</sub> 404.1407, found 404.1401 (Δ -1.5 ppm).

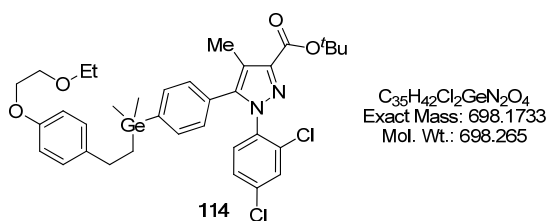
### Bromo-{2-[4-(2-ethoxyethoxy)phenyl]ethyl}(4-methoxyphenyl)-dimethylgermane **108**



To a solution of 4-[2-Dimethyl(4-methoxyphenyl)germylethyl]phenyl ethoxyethyl ether (3.87 g, 9.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added conc. HBr (3.0 mL, 48% wt.). The resulting biphasic reaction mixture was stirred for 16 h at RT, before being extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo* to give *bromo germane 108* as a yellow oil (3.57g, 99 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.73 (s, 6H, 2 × GeCH<sub>3</sub>), 1.24 (t, *J* = 7.0 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.54-1.59 (m, 2H, GeCH<sub>2</sub>CH<sub>2</sub>), 2.76-2.85 (m, GeCH<sub>2</sub>CH<sub>2</sub>), 3.60 (q, *J* = 7.0 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 3.78 (t, *J* = 5.0 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>O), 4.10 (t, *J* = 5.0 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>O), 6.86 (d, *J* = 8.7 Hz, 2H, ArH), 7.11 (d, *J* = 8.7 Hz, 2H, ArH); <sup>13</sup>C (100.7 MHz, CDCl<sub>3</sub>): δ 4.1 (2q), 15.2 (q), 23.9 (t), 29.6 (t), 66.8 (t), 67.5 (t), 69.0 (t), 114.7 (2d), 128.9 (2d), 135.0 (s), 157.2 (s); IR ν<sub>max</sub> (neat): 3010, 2875,

1600, 1580, 1510, 1500, 1455, 1280, 1250, 1105, 1050, 985, 860  $\text{cm}^{-1}$ ; MS ( $\text{EI}^+$ ) (rel. intensity) 376 [ $\text{M}(^{79}\text{Br})^+$ , 40], 348 (20), 224 (10), 193 (100), 179 (25), 121 (60); HRMS ( $\text{EI}^+$ ) calc'd for  $\text{C}_{14}\text{H}_{23}^{79}\text{Br}^{74}\text{GeO}_2$  376.0093, found 376.0085 ( $\Delta$  -2.2 ppm).

**1-(2,4-Dichlorophenyl)-5-[4-({2-[4-(2-ethoxyethoxy)phenyl]ethyl}-dimethylgermyl)phenyl]-4-methyl-1*H*-pyrazole-3-carboxylic acid *tert*-butyl ester**  
**114**

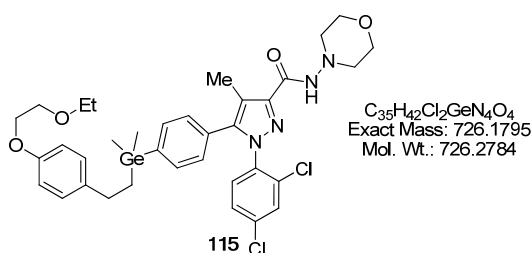


**Method F:** to a solution of  $i\text{PrMgCl}$  (100  $\mu\text{L}$ , 0.2 mmol, 2 M in THF) in THF (5.0 mL) at 0  $^\circ\text{C}$  was added a solution of  $n\text{BuLi}$  (160  $\mu\text{L}$ , 0.4 mmol, 2.5 M in hexanes) dropwise. After stirring at this temperature for 30 min a bimetallic  $i\text{Pr}^n\text{Bu}_2\text{MgLi}$  complex (0.04 M in THF) was formed as a pale yellow solution.<sup>217</sup> In a separate flask, a solution of pyrazole carboxylic acid *tert*-butyl ester **113** (56.3 mg, 0.117 mmol) and bromo germane **108** (51.2 mg, 0.136 mmol) in THF (10 mL) was cooled to -78  $^\circ\text{C}$  and the  $i\text{Pr}^n\text{Bu}_2\text{MgLi}$  solution (3.5 mL, 0.14 mmol, 0.04 M in THF) added to this dropwise. The resulting mixture was stirred at this temperature for 2 h and warmed to RT for 14 h. The mixture was diluted with  $\text{Et}_2\text{O}$  (50 mL) and a solution of 1.0 M  $\text{NH}_4\text{Cl}$  was added to the reaction mixture until no effervescence occurred. Following extraction with  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL), the combined the organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo*. The residue was purified by FC (EtOAc-Hexane, 15/85) to give *germyl pyrazole-3-carboxylic acid tert-butyl este* **114** as a pale yellow oil (32.7 mg, 40 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.33 (s, 6H,  $2 \times \text{GeCH}_3$ ), 1.20-1.26 (m, 5H,  $\text{CH}_3 + \text{GeCH}_2\text{CH}_2$ ), 1.64 [s, 9H,  $(\text{CH}_3)_3$ ], 2.30 (s, 3H,  $\text{CH}_3$ ), 2.57-2.64 (m, 2H,  $\text{GeCH}_2\text{CH}_2$ ), 3.60 (q,  $J = 7.0$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 3.78 (t,  $J = 5.0$  Hz,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.09 (t,  $J = 5.0$  Hz, 2H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 6.82 (d,  $J = 8.6$  Hz, 2H, ArH), 7.03 (d,  $J = 8.6$  Hz, 2H, ArH), 7.07 (d,  $J = 8.0$  Hz, 2H, ArH), 7.27 (dd,  $J = 8.4$ , 2.3 Hz, 1H, ArH), 7.35 (d,  $J = 8.0$  Hz, 2H, ArH), 7.37 (d,  $J = 8.6$  Hz, 2H, ArH);  $^{13}\text{C}$  (100.7 MHz,  $\text{CDCl}_3$ ):  $\delta$  -3.8 (2q), 10.1 (q), 15.2 (q), 17.9 (t), 28.3 (3q), 30.1 (t), 66.8

(t), 67.5 (t), 69.0 (t), 81.7 (s), 114.5 (2d), 118.1 (s), 127.6 (d), 128.6 (2d), 128.9 (2d), 130.0 (d), 130.8 (s), 130.9 (d), 133.1 (s), 133.2 (2d), 135.5 (s), 136.4 (s), 136.7 (s), 142.4 (s), 143.9 (s), 144.4 (s), 156.9 (s), 162.2 (s); IR  $\nu_{\text{max}}$  (neat): 3010, 2920, 1715, 1580, 1510, 1430, 1360, 1320, 1300, 1250, 1135, 1100, 1055, 1020, 965, 870; HRMS (ESI) calc'd for  $\text{C}_{35}\text{H}_{42}^{35}\text{Cl}_2^{74}\text{GeN}_2\text{O}_4\text{Na}$  ( $\text{MNa}$ )<sup>+</sup> 721.1631, found 721.1617 ( $\Delta$  -1.9 ppm).

**Method G:** A solution of pyrazole carboxylic acid tert-butyl ester **113** (523.0 mg, 1.085 mmol) containing 3 Å MS (200 mg) and bromo germane **108** (611 mg, 1.626 mmol) in THF (10 mL) was cooled to -78 °C and a solution of *t*-BuLi (1.74 mL, 2.436 mmol, 1.4 M in pentane) was added dropwise. The resulting mixture was stirred at this temperature for 2 h and warmed up to RT for 4 h. The mixture was diluted with Et<sub>2</sub>O (50 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred. Following extraction with Et<sub>2</sub>O (3 x 20 mL), combined the organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo*. The residue was purified by FC (EtOAc-Hexane, 15/85) to give *germyl pyrazole-3-carboxylic acid tert-butyl ester* **114** as a pale yellow oil (393.9 mg, 52 %). Analytical data as shown above.

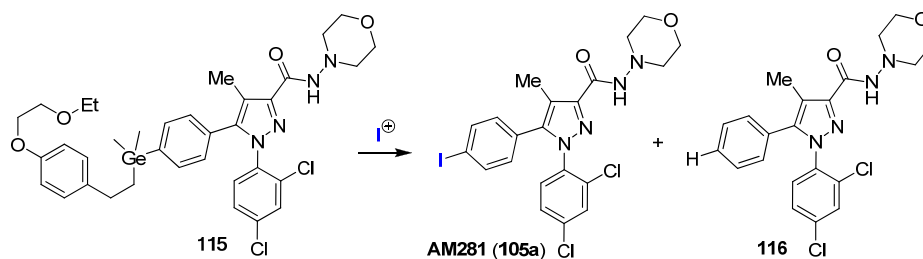
**1-(2,4-Dichloro-phenyl)-5-[4-({2-[4-(2-ethoxyethoxy)phenyl]ethyl}dimethylgermyl)phenyl]-4-methyl-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide **115****



According to the method of Lan,<sup>209</sup> to a solution of *germyl pyrazole-3-carboxylic acid tert-butyl ester* **114** (200 mg, 0.286 mmol) and *N*-aminomorpholine (43.82 mg, 41.4 μL, 0.429 mmol) in THF (5 mL) was added a solution of LHMDS (429 μL, 0.429 mmol, 1.0 M in hexanes) dropwise and stirred for 2 h at RT. The reaction mixture was diluted with Et<sub>2</sub>O (10 mL) and a solution of 1.0 M NH<sub>4</sub>Cl was added to the reaction mixture until no effervescence occurred. Following extraction with Et<sub>2</sub>O

(3 × 10 mL), the combined the organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo*. The residue was purified by FC (EtOAc-Hexane, 50/50) to give *germyl pyrazole-3-carboxylic acid morpholin-4-ylamide* **115** as a yellow oil (197.3 mg, 95 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.33 (s, 6H, 2 × GeCH<sub>3</sub>), 1.20-1.26 (m, 5H, CH<sub>3</sub>+GeCH<sub>2</sub>CH<sub>2</sub>), 2.38 (s, 3H, CH<sub>3</sub>), 2.57-2.64 (m, 2H, GeCH<sub>2</sub>CH<sub>2</sub>), 2.93-2.97 [m, 4H, N(CH<sub>2</sub>)<sub>2</sub>], 3.59 (q, *J* = 7.0 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 3.77 (t, *J* = 5.0 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>O), 3.84-3.87 [m, 4H, O(CH<sub>2</sub>)<sub>2</sub>], 4.08 (t, *J* = 5.0 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>O), 6.81 (d, *J* = 8.5 Hz, 2H, ArH), 7.02 (d, *J* = 8.5 Hz, 2H, ArH), 7.07 (d, *J* = 7.9 Hz, 2H, ArH), 7.27-7.30 (m, 2H, ArH), 7.37 (d, *J* = 7.9 Hz, 2H, ArH), 7.43 (d, *J* = 1.1 Hz, 1H, ArH), 7.72 (s, 1H, NH); <sup>13</sup>C (100.7 MHz, CDCl<sub>3</sub>): δ -3.8 (2q), 9.4 (q), 15.1 (q), 17.8 (t), 30.0 (t), 56.0 (2t), 66.5 (2t), 66.8 (t), 67.4 (t), 69.0 (t), 114.5 (2d), 118.1 (s), 127.7 (d), 128.2 (s), 128.6 (2d), 128.7 (2d), 130.2 (d), 130.6 (d), 133.1 (s), 133.3 (2d), 135.7 (s), 136.1 (s), 136.6 (s), 142.6 (s), 143.9 (s), 144.2 (s), 156.9 (s), 160.3 (s); IR (KBr): 3200, 3010, 2920, 2850, 1680, 1525, 1500, 1480, 1385, 1350, 1240, 1120, 1050, 965, 910, 810, 725 cm<sup>-1</sup>; HRMS (ESI) calc'd for C<sub>35</sub>H<sub>43</sub><sup>35</sup>Cl<sub>2</sub><sup>74</sup>GeN<sub>4</sub>O<sub>4</sub> (MH)<sup>+</sup> 727.1873, found 727.1890 (Δ 2.3 ppm).

Screening conditions for *ipso*-iododegermylation in solution phase (Table 3.4.1)



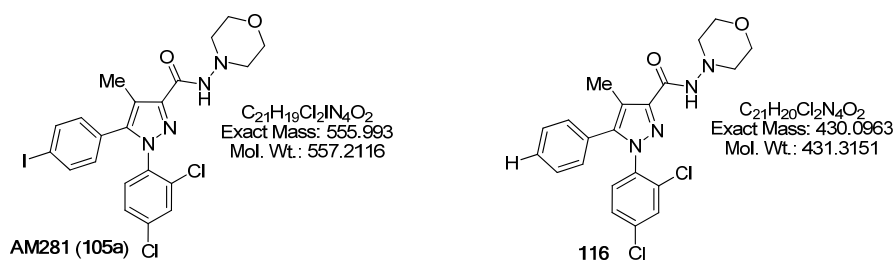
| Entry | Conditions <sup>a</sup>                              | Yield (%)       |
|-------|------------------------------------------------------|-----------------|
| 1     | NaI, chloramine T, AcOH, 16 h, RT                    | 0 <sup>c</sup>  |
| 2     | I <sub>2</sub> , CCl <sub>4</sub> , 16 h, RT         | 0 <sup>c</sup>  |
| 3     | NaI, FeCl <sub>3</sub> , 16 h, RT                    | 0 <sup>c</sup>  |
| 4     | ICl, 16 h, RT                                        | 0 <sup>c</sup>  |
| 5     | NH <sub>4</sub> I, Oxone <sup>®</sup> , 16 h, RT     | 0 <sup>c</sup>  |
| 6     | NaI, 3-CPBA, 16 h, RT <sup>b</sup>                   | 0 <sup>d</sup>  |
| 7     | NaI, AcO <sub>2</sub> H, AcOH, 16 h, RT <sup>b</sup> | 0 <sup>d</sup>  |
| 8     | I <sub>2</sub> , 3-CPBA, HOAc <sup>b</sup>           | 0 <sup>d</sup>  |
| 9     | NIS, TFA (cat.), HOAc, 16 h, RT                      | 0 <sup>d</sup>  |
| 10    | I <sub>2</sub> , HOAc, RT, 16 h                      | 15 <sup>e</sup> |
| 11    | I <sub>2</sub> , TFA-HOAc, 16 h, RT <sup>f</sup>     | 63 <sup>e</sup> |
| 12    | NaI, NCS, TFA-AcOH, 30 min, RT <sup>f</sup>          | 85              |

<sup>a</sup>All reactions were carried out with 2 eq of reagents. <sup>b</sup>slow addition of peracids in CH<sub>2</sub>Cl<sub>2</sub> (50 μL/min for 30 min) <sup>c</sup>No reaction occurred, recovery of S.M. <sup>d</sup>Decomposition of S.M. <sup>e</sup>concomitant with by-product **116**. <sup>f</sup>TFA-HOAc (1:3 v/v).

*Representative procedures for screening ipso-iododegermylation conditions:*

**1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide **AM281 (105a)****<sup>209</sup> and

**1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide **116****



*Entry 10:*

To a solution of *germyl pyrazolyl morpholin-4-ylamide* **115** (20 mg, 27.54  $\mu$ mol) in HOAc (5mL) was added I<sub>2</sub> (14 mg, 55.12  $\mu$ mol). The reaction mixture was stirred at RT for the indicated time until complete consumption of starting material **115** as monitored by TLC. The resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and H<sub>2</sub>O (10 mL), followed by addition of solid NaS<sub>2</sub>O<sub>5</sub> until a colourless solution formed. At this point, the pH of the solution was adjusted with solid K<sub>2</sub>CO<sub>3</sub> to pH 8.0. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL) and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo*. The residue was purified by FC (EtOAc-Hexane, 50/50) to afford:

*Iodinated pyrazole-3-carboxylic acid morpholin-4-ylamide* **AM281 (105a)** as an orange solid ( 2.3 mg, 15 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  2.34 (s, 3H, CH<sub>3</sub>), 2.90-2.94 [m, 4H, N(CH<sub>2</sub>)<sub>2</sub>], 3.80-3.85 [m, 4H, O(CH<sub>2</sub>)<sub>2</sub>], 6.83 (d, *J* = 8.4 Hz, 2H, ArH), 7.27-7.29 (m, 2H, ArH), 7.41 (d, *J* = 1.9 Hz, 1H, ArH), 7.63 (d, *J* = 8.4 Hz, 2H, ArH), 7.69 (s, 1H, NH); <sup>13</sup>C (100.7 MHz, CDCl<sub>3</sub>):  $\delta$  9.2 (q), 55.9 (2t), 66.4 (2t), 95.1 (s), 118.2 (s), 127.9 (d), 128.0 (s), 130.3 (d), 130.5 (d), 131.0 (2d), 132.8 (s), 135.7 (s), 136.0 (s), 137.7 (2d), 143.1 (s), 144.0 (s), 160.0 (s); HRMS (ESI) calc'd for C<sub>21</sub>H<sub>20</sub>Cl<sub>2</sub>IN<sub>4</sub>O<sub>2</sub> (MH)<sup>+</sup> 557.0008, found 557.0022 ( $\Delta$  2.5 ppm).

*Protodegermylation by-product* **116** as a pale yellow solid (1.2 mg, 10 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  2.36 (s, 3H, CH<sub>3</sub>), 2.93-2.97 [m, 4H, N(CH<sub>2</sub>)<sub>2</sub>],

3.84-3.86 [m, 4H, O(CH<sub>2</sub>)<sub>2</sub>], 7.08-7.14 (m, 2H, ArH), 7.26 (m, 2H, ArH), 7.28-7.32 (m, 3H, ArH), 7.40(s, 1H, ArH), 7.73 (s, 1H, NH); <sup>13</sup>C (100.7 MHz, CDCl<sub>3</sub>): δ 9.3 (q), 56.0 (2t), 66.4 (2t), 118.0 (s), 127.7 (d), 128.3 (s), 128.4 (2d), 128.7 (d), 129.5 (2d), 130.2 (d), 130.5 (d), 133.0 (s), 135.8 (s), 136.0 (s), 143.8 (s), 144.2 (s), 160.3 (s); HRMS (ESI) calc'd for C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>2</sub> (MH)<sup>+</sup> 431.1042, found 431.1044 (Δ 0.5 ppm).

*Entry 11:*

To a solution of *germyl pyrazolyl morpholin-4-ylamide* **115** (25.2 mg, 34.7 μmol) in TFA-HOAc (5 mL, 1:3 v/v) was added I<sub>2</sub> (17.6 mg, 69.5 μmol). The reaction mixture was stirred at RT for the indicated time until complete consumption of starting material **115** as monitored by TLC. The resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and H<sub>2</sub>O (10 mL), followed by addition of solid NaS<sub>2</sub>O<sub>5</sub> until a colourless solution formed. At this point, the pH of the solution was adjusted with solid K<sub>2</sub>CO<sub>3</sub> to pH 8.0. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL) and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo*. The residue was purified by FC (EtOAc-Hexane, 50/50) to afford *iodinated pyrazole* **AM281 (105a)** as an orange solid (12.2 mg, 63 %) and *protodegermylation by-product* **116** (1.5 mg, 10 %). Analytical data as shown above.

*Entry 12:*

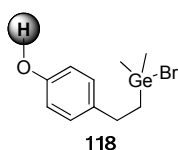
To a solution of *germyl pyrazolyl morpholin-4-ylamide* **115** (23.0 mg, 31.7 μmol) and NaI (9.5 mg, 63.5 μmol) in TFA-HOAc (5 mL, 1:3 v/v) were added NCS (8.5 mg, 63.5 μmol) and stirred for 30 min at RT. The resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and H<sub>2</sub>O (10 mL), followed by addition of solid NaS<sub>2</sub>O<sub>5</sub> until a colourless solution formed. At this point, the pH of the solution was adjusted with solid K<sub>2</sub>CO<sub>3</sub> to pH 8.0. Purification by FC (EtOAc-Hexane, 50/50) gave desired *iodinated pyrazole-3-carboxylic acid morpholin-4-ylamide* **AM281 (105a)** as an orange solid (20.8 mg, 85 %). No *protodegermylation by-product* **116** was found under the conditions. Analytical data as shown above.

### HypoGel<sup>®</sup>-Br **117**<sup>138</sup>



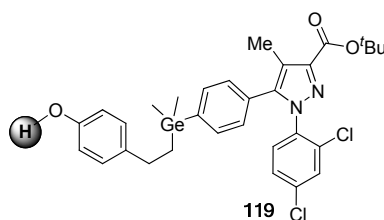
To a suspension of HypoGel<sup>®</sup>-200-OH (20.0 g, LL = 0.8 mmol g<sup>-1</sup>, 16.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C was added triphenylphosphine (8.34 g, 32 mmol) and carbon tetrabromide (21.22 g, 64 mmol). The resulting yellow suspension was warmed to RT and stirred for 24 h. The solvent was then removed by filtration and the resin was washed with H<sub>2</sub>O (3 × 100 mL), MeOH (3 × 100 mL), THF (3 × 100 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL). The resulting resin as dried *in vacuo* at 50 °C for 16 h to furnish *bromo resin 117* as yellow grains (21.0 g, LL = 0.8 mmol g<sup>-1</sup> was determined by the weight increase of the resin); IR  $\nu_{\max}$  (KBr): 3060, 3020, 2890, 1944, 1875, 1805, 1750, 1600, 1490, 1455, 1355, 1295, 1105. 980, 890 cm<sup>-1</sup>.

### HypoGel<sup>®</sup>-dimethylgermyl bromide **118**



A suspension of HypoGel<sup>®</sup>-Br **117** (5.0 g, LL = 0.8 mmol g<sup>-1</sup>, 4 mmol), K<sub>2</sub>CO<sub>3</sub> (2.76 g, 20 mmol), TBAI (1.48 g, 4 mmol) and *dimethylgermyl phenol 107* (3.31 g, 10 mmol) in DMF (15 mL) was heated to 80 °C for 24 h. The solvent was removed by filtration and the resin was then washed with H<sub>2</sub>O (3 × 20 mL), MeOH (3 × 20 mL), THF (3 × 20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The resulting *dimethyl-4-anisoyl germyl resin* was swollen in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and conc. HBr (2.0 mL, 48% wt.) added. The reaction mixture was stirred for 16 h at RT followed by filtration to remove the solvent. The resin was successively rinsed with H<sub>2</sub>O (3 × 20 mL), MeOH (3 × 20 mL), THF (3 × 20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL) and then dried *in vacuo* at 50 °C for 16 h to give *dimethylgermyl bromide resin 118* as light brown granules (5.84 g, LL = 0.75 mmol g<sup>-1</sup> as determined by the mass of anisole by-product recovered). IR  $\nu_{\max}$  (KBr): 3050, 3010, 2930, 1950, 1840, 1600, 1450, 1110, 960, 850 cm<sup>-1</sup>.

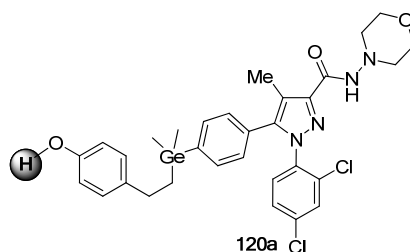
### HypoGel<sup>®</sup>-dimethylgermylpyrazole-*tert*-butyl ester **119**



To a suspension of HypoGel<sup>®</sup>-dimethylgermyl bromide **118** (5.0 g, LL = 0.75 mmol g<sup>-1</sup>, 3.75 mmol) and pyrazole carboxylic acid *tert*-butyl ester **113** (3.62 g, 7.5 mmol) in THF (20 mL) was cooled to -78 °C and a solution of *t*-BuLi (6.03 mL, 8.44 mmol, 1.4 M in pentane) added dropwise. The reaction mixture was stirred at this temperature for 2 h, warmed to RT and stirred for further 14 h. A solution of 1.0 M NH<sub>4</sub>Cl was added until no effervescence occurred, and then the solvent was removed by filtration and the resin was then washed with H<sub>2</sub>O (3 × 20 mL), MeOH (3 × 20 mL), THF (3 × 20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL) to afford *dimethylgermyl-pyrazole-tert-butyl ester resin 119* as brown granules (5.66 g, 55 % conversion was determined by the weight increase of the resin and the mass of recovered debrominated pyrazole carboxylic acid *tert*-butyl ester, LL = 0.42 mmol g<sup>-1</sup>); IR  $\nu_{\text{max}}$  (KBr): 3050, 3010, 2920, 1940, 1830, 1670, 1650, 1600, 1505, 1455, 1242, 1100, 980, 860 cm<sup>-1</sup>.

*General procedure for the preparation of HypoGel<sup>®</sup>- aryl pyrazolyl germanes **120** (Scheme 3.4.9)*

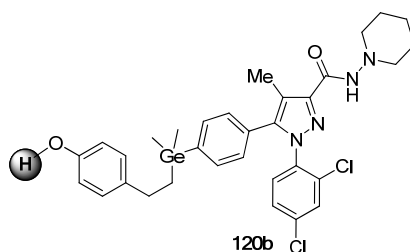
### HypoGel<sup>®</sup>-dimethylgermyl-pyrazole carboxylic acid morpholin-4-ylamide **120a**



To a suspension of HypoGel<sup>®</sup>- dimethylgermyl-pyrazole-*tert*-butyl ester **119** (0.5 g, 0.21 mmol, LL = 0.42 mmol g<sup>-1</sup>) and *N*-aminomorpholine (107.3 mg, 101  $\mu$ L, 1.05 mmol) in THF (5 mL) was added a solution of LHNDS (1.16  $\mu$ L, 1.16 mmol, 1.0 M

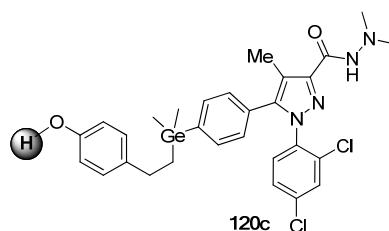
in THF) dropwise and the resulting suspension stirred for 16 h at RT. The solvent was removed by filtration and the resin was then washed with H<sub>2</sub>O (3 × 20 mL), MeOH (3 × 20 mL), THF (3 × 20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL) to afford *pyrazole morpholin-4-ylamide resin 120a* as brown grains [0.5 g, LL = 0.42 mmol g<sup>-1</sup>, as determined by swelling a sample of the resin (30.0 mg) in CH<sub>2</sub>Cl<sub>2</sub> and adding of conc. HBr (1.0 mL, 48% wt.) for 1 h at RT to achieve the protonolysis of the resin to give corresponding protonated *pyrazolyl morpholin-4-ylamide 116* (5.4 mg, 12.52 mmol)]. IR (KBr): 3450 (brs), 3020, 1945, 1800, 1670, 1655, 1600, 1560, 1450, 1350, 1300, 1245, 1195, 1100, 860, 755 cm<sup>-1</sup>

#### HypoGel<sup>®</sup>-dimethylgermyl-pyrazole carboxylic acid piperidin-1-ylamide **120b**



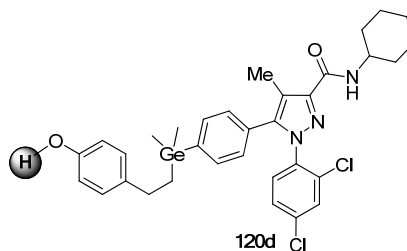
Using the *general procedure*, HypoGel<sup>®</sup>- dimethylgermyl-pyrazole-*tert*-butyl ester **119** (0.45 g, 0.189 mmol, LL = 0.42 mmol g<sup>-1</sup>), *N*-aminopiperidine (94.7 mg, 102 μL, 0.945 mmol) and a solution of LHMDS (1.04 mL, 1.04 mmol, 1.0 M in hexanes) were employed. The solvent was removed by filtration and the resin was washed successively with H<sub>2</sub>O (3 × 20 mL), MeOH (3 × 20 mL), THF (3 × 20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL) to give *pyrazole piperidin-1-ylamide resin 120b* as brown grains (0.45 g, LL = 0.42 mmol g<sup>-1</sup>). IR (KBr): 3420 (brs), 3020, 1940, 1875, 1805, 1690, 1600, 1500, 1490, 1350, 1300, 1245, 1200, 1100, 890, 755 cm<sup>-1</sup>.

**HypoGel<sup>®</sup>-dimethylgermyl-pyrazole carboxylic acid *N,N'*-dimethylhydrazide 120c**



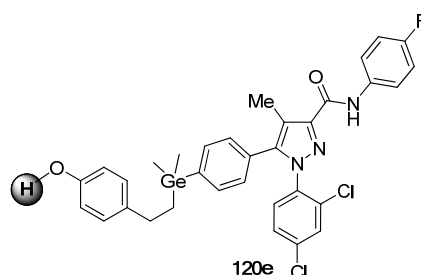
Using the *general procedure*, HypoGel<sup>®</sup>- dimethylgermyl-pyrazole-*tert*-butyl ester **119** (0.5 g, 0.21 mmol, LL = 0.42 mmol g<sup>-1</sup>), *N,N'*-dimethylhydrazine (63.1 mg, 80  $\mu$ L, 1.05 mmol) and a solution of LHMDs (1.16  $\mu$ L, 1.16 mmol, 1.0 M in hexanes) were employed. The solvent was removed by filtration and the resin was washed successively with H<sub>2</sub>O (3  $\times$  20 mL), MeOH (3  $\times$  20 mL), THF (3  $\times$  20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  20 mL) to afford *pyrazole N,N'*-dimethylhydrazide resin **120c** as brown grains (0.5 g, LL = 0.42 mmol g<sup>-1</sup>). IR (KBr): 3450 (brs), 3020, 2920, 1940, 1870, 1800, 1670, 1600, 1500, 1490, 1455, 1350, 1245, 1110, 900, 755 cm<sup>-1</sup>.

**HypoGel<sup>®</sup>-dimethylgermyl-pyrazole carboxylic acid cyclohexylamide 120d**



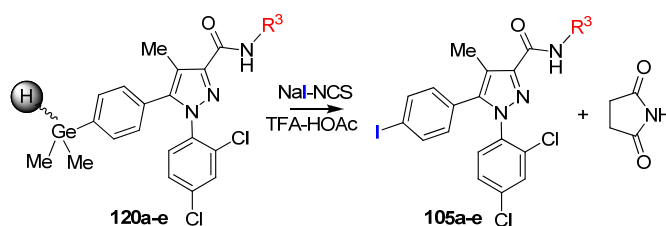
Using the *general procedure*, HypoGel<sup>®</sup>- dimethylgermyl-pyrazole-*tert*-butyl ester **119** (0.5 g, 0.21 mmol, LL = 0.42 mmol g<sup>-1</sup>), 4-fluoroaniline (104 mg, 120  $\mu$ L, 1.05 mmol) and a solution of LHMDs (1.16  $\mu$ L, 1.16 mmol, 1.0 M in hexanes) were employed. The solvent was removed by filtration and the resin was washed successively by H<sub>2</sub>O (3  $\times$  20 mL), MeOH (3  $\times$  20 mL), THF (3  $\times$  20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  20 mL) to give *pyrazole cyclohexylamide resin* **120d** as brown grains (0.45 g, LL = 0.38 mmol g<sup>-1</sup>). IR (KBr): 3420 (brs), 3050, 3010, 2920, 1945, 1875, 1800, 1650, 1600, 1500, 1455, 1350, 1245, 1195, 1100, 765 cm<sup>-1</sup>.

## HypoGel<sup>®</sup>-dimethylgermyl-pyrazole carboxylic acid 4-fluorophenylamide **120e**



Using the *general procedure*, HypoGel<sup>®</sup>-dimethylgermyl-pyrazole-*tert*-butyl ester **119** (0.5 g, 0.21 mmol, LL = 0.42 mmol g<sup>-1</sup>), cyclohexylamine (116.7 mg, 100  $\mu$ L, 1.05 mmol) and a solution of LHMDs (1.16  $\mu$ L, 1.16 mmol, 1.0 M in hexanes) were employed. The solvent was removed by filtration and the resin was washed successively with H<sub>2</sub>O (3  $\times$  20 mL), MeOH (3  $\times$  20 mL), THF (3  $\times$  20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  20 mL) to afford *pyrazole 4-fluorophenylamide resin 120e* as dark red grains (0.43 g, LL = 0.35 mmol g<sup>-1</sup>). IR (KBr): 3380 (brs), 3045, 3015, 2920, 1945, 1870, 1805, 1645, 1600, 1500, 1455, 1350, 1300, 1245, 1100, 785 cm<sup>-1</sup>.

## Rapid preparation of iodinated cannabinoid receptor ligands through *ipso*-iododegermylation (Table 3.4.2)



| Entry | Substrate   | Time (h) | Product             | Yield (%)               | Overall yield (%) |
|-------|-------------|----------|---------------------|-------------------------|-------------------|
| 1     | <b>120a</b> | 1        | <b>AM281 (105a)</b> | 63                      | 38                |
| 2     | <b>120b</b> | 1        | <b>AM251 (105b)</b> | 60                      | 33                |
| 3     | <b>120c</b> | 1        | <b>105c</b>         | 60                      | 33                |
| 4     | <b>120d</b> | 1        | <b>105d</b>         | 55                      | 28                |
| 5     | <b>120e</b> | 6        | <b>105e</b>         | 42                      | 19                |
| 6     | <b>120b</b> | 5 min    | <b>AM251 (105b)</b> | 8 (1 <sup>st</sup> run) | 4.4               |
| 7     | <b>120b</b> | 5 min    | <b>AM251 (105b)</b> | 5 (2 <sup>nd</sup> run) | 2.8               |

*Typical procedure for ipso-iododegermylation:*

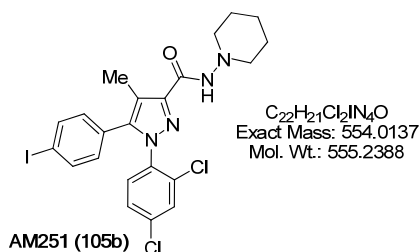
**1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide AM281 (105a)**

*Entry 1:*

Pyrazole morpholin-4-ylamide resin **120a** (52 mg, 0.022  $\mu$ mol, LL = 0.42 mmol g<sup>-1</sup>) and NaI (16.4 mg, 0.11 mmol) were suspended in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) in a cartridge and a solution of NCS (11.7 mg, 0.087 mmol) in TFA-HOAc (5 mL, 1:3 v/v) were added. The reaction mixture was shaken at RT for the indicated time. The solvent was removed by filtration and the resin washed with H<sub>2</sub>O (3  $\times$  10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL). Solid Na<sub>2</sub>SO<sub>5</sub> was then added to the collected organic filtrate until a colourless solution formed. The pH of this solution was adjusted to pH 8.0 with K<sub>2</sub>CO<sub>3</sub>. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL) and combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo*. The residue was purified by FC (hexane/EtOAc, 50/50) to afford *iodinated pyrazole-3-carboxylic acid morpholin-4-ylamide AM281 (105a)* as a white solid (7.7 mg, 63 %). Analytical data as shown above.

**1-(2,4-Dichloro-phenyl)-5-(4-iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide AM251 (105b)<sup>221</sup>**

*Entry 2:*

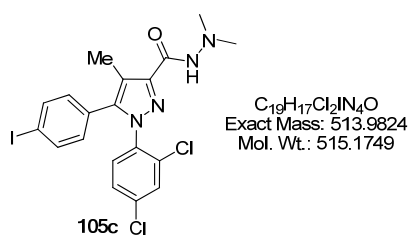


Using the *typical procedure* described for entry 1, pyrazole piperidin-1-ylamide resin **120b** (55.2 mg, 0.023 mmol, LL = 0.42 mmol g<sup>-1</sup>), NaI (17.2 mg, 0.115 mmol) and NCS (12.3 mg, 0.092 mmol) were employed. The collected organic filtrate was analyzed by HPLC prior to purification by FC (hexane/EtOAc, 50/50) to give *iodinated pyrazole-3-carboxylic acid piperidin-1-ylamide AM251 (105b)* (7.7 mg,

60 %) as a pale yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.34-1.47 (m, 2H,  $\text{CH}_2$ ), 1.67-1.77 (m, 4H,  $2\times\text{CH}_2$ ), 2.35 (s, 3H,  $\text{CH}_3$ ), 2.76-2.92 [m, 4H,  $\text{N}(\text{CH}_2)_2$ ], 6.84 (d,  $J = 8.4$  Hz, 2H, ArH), 7.27-7.30 (m, 2H, ArH), 7.42 (d,  $J = 1.8$  Hz, 2H, ArH), 7.64 (d,  $J = 8.4$  Hz, 3H, NH+ArH);  $^{13}\text{C}$  (100.7 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.3 (q), 23.3 (t), 25.4 (2t), 57.1 (2t), 95.0 (s), 118.2 (s), 127.9 (d), 128.2 (s), 130.3 (d), 130.5 (d), 131.1 (2d), 132.9 (s), 135.8 (s), 135.9 (s), 137.7 (2d), 143.0 (s), 144.4 (s), 160.0 (s); HRMS (ESI) calc'd for  $\text{C}_{22}\text{H}_{22}\text{Cl}_2\text{IN}_4\text{O}$  ( $\text{MH}$ ) $^+$  555.0215, found 555.0227 ( $\Delta$  2.2 ppm).

**1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid *N,N'*-dimethylhydrazide **105c****

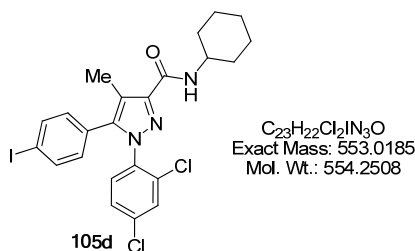
Entry 3:



Using the *typical procedure* described for entry 1, *N,N'*-dimethylhydrazide resin **120c** (43 mg, 0.018 mmol, LL = 0.42 mmol  $\text{g}^{-1}$ ), NaI (13.5 mg, 0.09 mmol) and NCS (9.6 mg, 0.072 mmol) were employed. Purification by FC (EtOAc/Hexane, 50/50) gave *iodinated pyrazole-3-carboxylic acid N,N'*-dimethyl-hydrazide **105c** as a white solid (5.5 mg, 60 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.33 (s, 3H,  $\text{CH}_3$ ), 2.67 [s, 6H,  $\text{N}(\text{CH}_3)_2$ ], 6.82 (d,  $J = 8.3$  Hz, 2H, ArH), 7.25-7.28 (m, 2H, ArH), 7.39 (d,  $J = 1.4$  Hz, 1H, ArH), 7.62 (d,  $J = 8.3$  Hz, 3H, NH+ArH);  $^{13}\text{C}$  (100.7 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.3 (q), 47.5 (2q), 95.0 (s), 118.0 (s), 127.8 (d), 128.0 (s), 130.2 (d), 130.4 (d), 131.0 (2d), 132.8 (s), 135.7 (s), 135.9 (s), 137.6 (2d), 142.9 (s), 144.1 (s), 160.2 (s); HRMS (ESI) calc'd for  $\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{IN}_4\text{O}$  ( $\text{MH}$ ) $^+$  514.9902, found 514.9905 ( $\Delta$  0.6 ppm).

**1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid cyclohexylamide **105d****

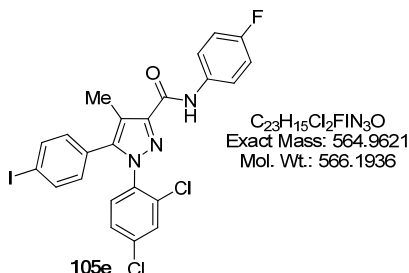
Entry 4:



Using the *typical procedure* described in entry 1, pyrazole cyclohexylamide resin **120d** (65 mg, 0.0247 mmol, LL = 0.35 mmol g<sup>-1</sup>), NaI (18.5 mg, 0.124 mmol) and NCS (13.2 mg, 0.099 mmol) were employed. Purification by FC (hexane/EtOAc, 50/50) gave *iodinated pyrazole-3-carboxylic acid cyclohexyl-amide* **105d** as a white solid (7.5 mg, 55 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.19-1.30 (m, 3H, 3xCH), 1.35-1.45 (m, 2H, CH<sub>2</sub>), 1.60-1.66 (m, 1H, CH), 1.72-1.77 (m, 2H, CH<sub>2</sub>), 1.98-2.01 (m, 2H, CH<sub>2</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 3.89-3.99 (m, 1H, CH), 6.85 (d, *J* = 8.4 Hz, 3H, NH+ArH), 7.29 (s, 2H, ArH), 7.42 (s, 1H, ArH), 7.64 (d, *J* = 8.4 Hz, 2H, ArH); <sup>13</sup>C (100.7 MHz, CDCl<sub>3</sub>): δ 9.4 (q), 25.0 (2t), 25.6 (t), 33.2 (2t), 47.9 (d), 94.9 (s), 117.7 (s), 127.9 (d), 128.3 (s), 130.3 (d), 130.6 (d), 131.1 (2d+s), 132.9 (s), 135.9 (s), 137.7 (2d), 143.1 (s), 145.2 (s), 161.7 (s); HRMS (ESI) calc'd for C<sub>23</sub>H<sub>23</sub>Cl<sub>2</sub>IN<sub>3</sub>O (MH)<sup>+</sup> 554.0263, found 554.0269 (Δ 1.1 ppm).

**1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid 4-fluorophenylamide **105e****

Entry 5:



Using the *typical procedure* described for entry 1, pyrazole (4-fluorophenyl)amide resin **120e** (102 mg, 0.0357 mmol, LL = 0.35 mmol g<sup>-1</sup>), NaI (26.8 mg, 0.179 mmol) and NCS (20.0 mg, 0.15 mmol) were employed. Purification by FC (hexane/EtOAc, 50/50) gave *iodinated pyrazole-3-carboxylic acid (4-fluoro-phenyl)amide* **105e** as a white solid (8.5 mg, 42 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.42 (s, 3H, CH<sub>3</sub>), 6.89 (d, *J* = 8.3 Hz, 2H, ArH), 7.00-7.07 (m, 2H, ArH), 7.29-7.34 (m, 2H, ArH), 7.45 (d, *J* = 1.8 Hz, 1H, ArH), 7.60-7.65 (m, 2H, ArH), 7.67 (d, *J* = 8.3 Hz, 2H, ArH), 8.76 (s, 1H, NH); <sup>13</sup>C (100.7 MHz, CDCl<sub>3</sub>): δ 9.5 (q), 95.2 (s), 114.9 (s), 115.6 (2d, <sup>2</sup>*J*<sub>C-F</sub> = 22.5 Hz), 118.2 (s), 121.4 (2d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz), 124.9 (s), 127.9 (d), 130.4 (d), 130.5 (d), 131.1 (2d), 133.0 (s), 133.8 (s), 135.7 (s), 136.2 (s), 137.8 (2d), 144.2 (d, <sup>1</sup>*J*<sub>C-F</sub> = 109.2 Hz), 160.4 (s); <sup>19</sup>F NMR (367 MHz, CDCl<sub>3</sub>): δ -118.1 (s, 1F); HRMS (ESI) calc'd for C<sub>23</sub>H<sub>16</sub>Cl<sub>2</sub>IN<sub>3</sub>O (MH)<sup>+</sup> 565.9699, found 565.9693 (Δ -1.1 ppm).

**1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide AM251 (**105b**)**

Entry 6:

Using the *typical procedure* described for entry 1, pyrazole piperidin-1-ylamide resin **120b** (102.1 mg, 0.0429 mmol, LL = 0.42 mmol g<sup>-1</sup>), NaI (32.1 mg, 0.214 mmol) and NCS (22.9 mg, 0.172 mmol) were employed. The reaction mixture was shaken for 5 min at RT followed by filtration to remove the resin. Purification by PLC (hexane/EtOAc, 50/50) gave *iodinated pyrazole-3-carboxylic acid*

*piperidin-1-ylamide* **AM251 (105b)** (1.9 mg, 8 %) as a pale yellow solid. Analytical data as described previously.

*Entry 7:*

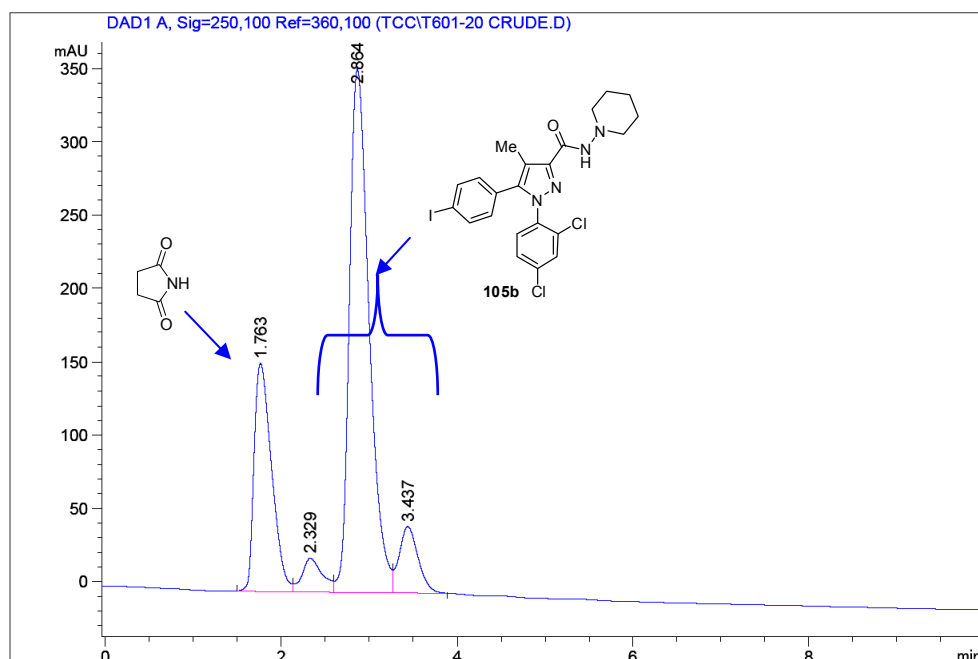
The recovered pyrazole piperidin-1-ylamide resin **120b** from *entry 6* was re-subjected to the identical conditions at RT for 5 min. The filtration liquid was collected and purified by PLC (EtOAc-Hexane, 50/50) to give *iodinated pyrazole-3-carboxylic acid piperidin-1-ylamide* **AM251 (105b)** (1.1 mg, 5 %). Analytical data as described previously.

*HPLC analysis of the crude filtrate obtained from pyrazole piperidin-1-ylamide resin 120b (Table 3.4.2, entry 2)*

The crude filtrate of iodinated pyrazole **105b** was analyzed by HPLC as follows:

Column: XTerra RP-8, 4.6 mm × 150 mm, 5 μm; Mobile phase: 0.1 % TFA/MeCN : H<sub>2</sub>O = 70 : 30; Flow rate: 1 mL/min; Detection: UV diode array at 250 nm; Injection volume: 5 μL.

The ratio of the peak areas (75 %) was calculated for *iodinated product 105b* and by-product succinimide (Scheme 4.3.1). The three signals for the iodinated product **105b** are attributed to rotameric isomers of this compound (see Section 3.1.3).



#### Area Percent Report

Sorted By : Signal  
Multiplier: : 1.0000  
Dilution: : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

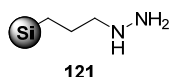
Signal 1: DAD1 A, Sig=250,100 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 1.763         | BV   | 0.2140      | 2160.92017   | 155.66649    | 24.5959 |
| 2      | 2.329         | VV   | 0.2349      | 374.28473    | 23.11868     | 4.2602  |
| 3      | 2.864         | VV   | 0.2396      | 5560.31934   | 357.17981    | 63.2884 |
| 4      | 3.437         | VB   | 0.2287      | 690.15460    | 45.57219     | 7.8554  |

Totals : 8785.67883 581.53717

**Scheme 4.3.1.** HPLC chromatography of crude filtrate of iodinated **105b**.

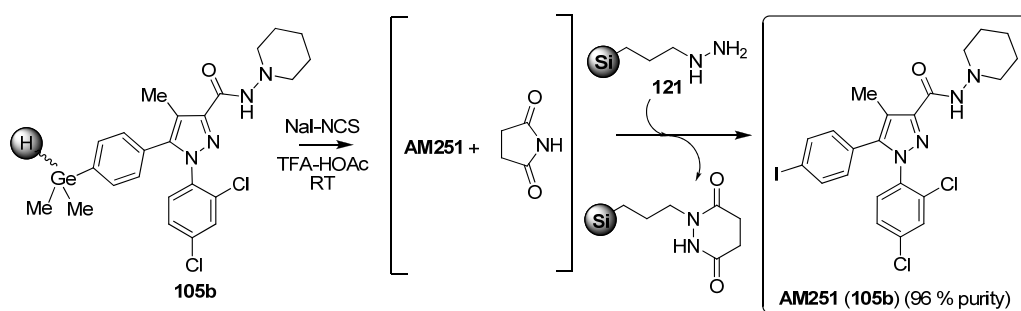
### ***Si*-propyl hydrazine resin **121****



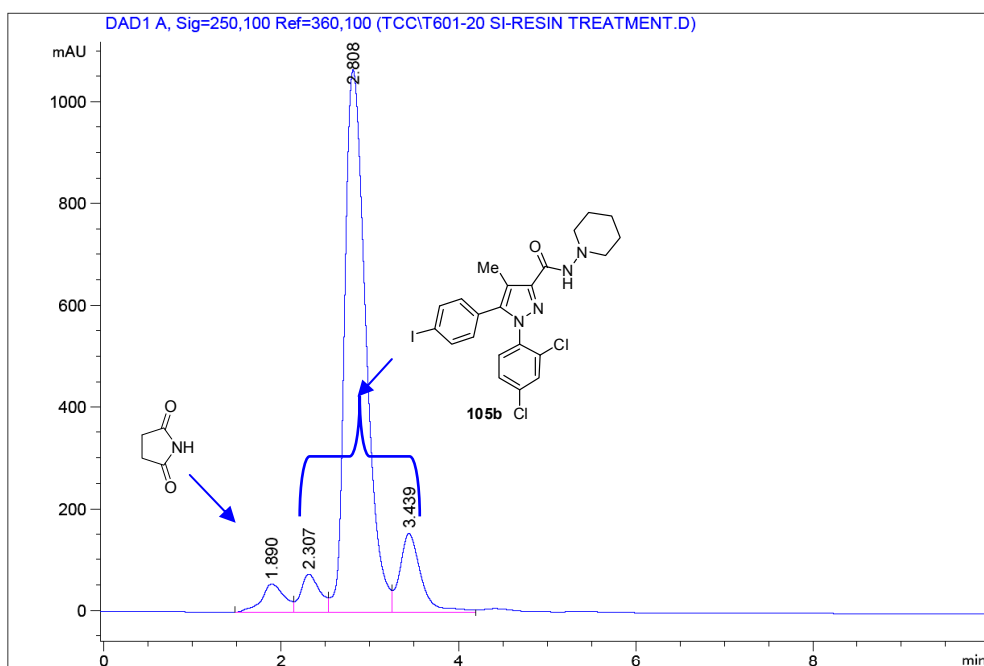
To a suspension of *Si*-propyl bromide resin (0.50 g, LL = 1.43 mmol g<sup>-1</sup>, 0.715 mmol) in DMF (10 mL) was added K<sub>2</sub>CO<sub>3</sub> (0.98 g, 7.1 mmol), NaI (1.07 g, 7.1 mmol) and hydrazine hydrate (230 mg, 7.1 mmol, 223 μL). The mixture was warmed to 80 °C

for 24 h. The solvent was then removed by filtration and the resin was washed with H<sub>2</sub>O (3 × 100 mL), EtOH (3 × 100 mL), THF (3 × 100 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL). The resulting resin was dried *in vacuo* at RT for 16 h to furnish *Si-hydrazine resin* **121** as white particles (0.466 g, LL = 1.43 mmol g<sup>-1</sup>, as determined by the weight loss of the resin) ; IR (KBr): 3450 (brs), 3300 (brs), 2950, 1630, 1405, 1110 cm<sup>-1</sup>.

*Sequential ipso-iododegermylation/succinimide scavenging protocol (Scheme 3.4.10)*



Using the typical iodination procedure described above, pyrazole piperidin-1-ylamide resin **105b** (25.1 mg, 0.0105 mmol, LL = 0.42 mmol g<sup>-1</sup>), NaI (7.9 mg, 0.0527 mmol) and NCS (5.6 mg, 0.042 mmol) were employed. The collected organic filtrate was dried *in vacuo* and re-suspended in EtOH (5 mL) in the presence the Si-propyl hydrazine resin **121** (150 mg, 0.215 mmol). The amount of succinimide scavenging resin **121** was employed based on the theoretical amount of NCS expected to remain. The mixture was then refluxed at 80 °C for 1 h. The resin was then filtered off and the filtrate analysed by HPLC. The chromatogram revealed a significant improvement in purity (96 %) of the desired product **105b**; relative to that obtained without the use of the succinimide scavenger resin (Scheme 4.3.2).



=====  
Area Percent Report  
=====

Sorted By : Signal  
Multiplier: : 1.0000  
Dilution: : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=250,100 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 1.890         | BV   | 0.2638      | 986.51813    | 54.86173     | 4.4319  |
| 2      | 2.307         | VV   | 0.2201      | 1116.29724   | 74.80441     | 5.0149  |
| 3      | 2.808         | VV   | 0.2586      | 1.75952e4    | 1066.07666   | 79.0456 |
| 4      | 3.439         | VB   | 0.2457      | 2561.54492   | 154.25052    | 11.5076 |

Totals : 2.22596e4 1349.99332

**Scheme 4.3.2.** HPLC chromatography of crude filtrate of iodinated **105b** after Si-hydrazine resin **121** treatment.

## Appendix 1: Solvent purification

All solvents were distilled before use. Petrol refers to fraction of petroleum-ether collected between 40-60 °C. Commercial grade solvents used for flash chromatography were used without further purification.

Anhydrous solvents were obtained as follows:

|                                     |                                                                                                                       |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>CH<sub>2</sub>Cl<sub>2</sub></b> | distilled from CaH <sub>2</sub> under N <sub>2</sub> immediately prior to use.                                        |
| <b>1,4-Dioxane</b>                  | distilled from sodium/benzophenone ketyl under N <sub>2</sub> immediately prior to use.                               |
| <b>Degassed DMF</b>                 | N <sub>2</sub> gas was purged through DMF for 30 min followed by degassed under high vacuum immediately prior to use. |
| <b>Et<sub>2</sub>O</b>              | distilled from sodium/benzophenone ketyl under N <sub>2</sub> immediately prior to use.                               |
| <b>EtOH</b>                         | commercially supplied HPLC grade.                                                                                     |
| <b>MeCN</b>                         | commercially supplied HPLC grade.                                                                                     |
| <b>MeOH</b>                         | commercially supplied HPLC grade.                                                                                     |
| <b>THF</b>                          | distilled from sodium/benzophenone ketyl under N <sub>2</sub> immediately prior to use.                               |
| <b>Toluene</b>                      | distilled from sodium under N <sub>2</sub> immediately before use.                                                    |

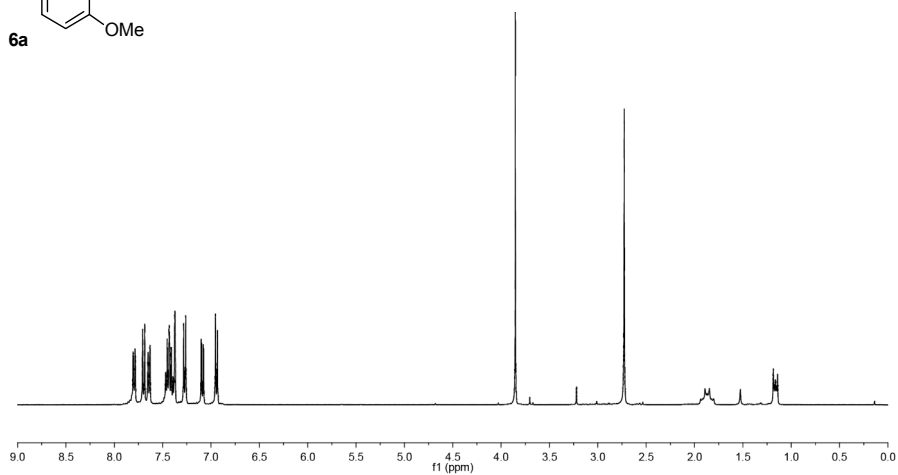
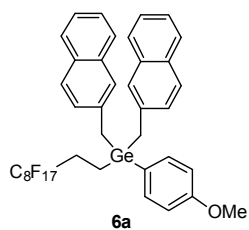
## Appendix 2: Reagent purification

Reagents were used as commercially supplied unless otherwise stated and handled in accordance with COSHH regulations.

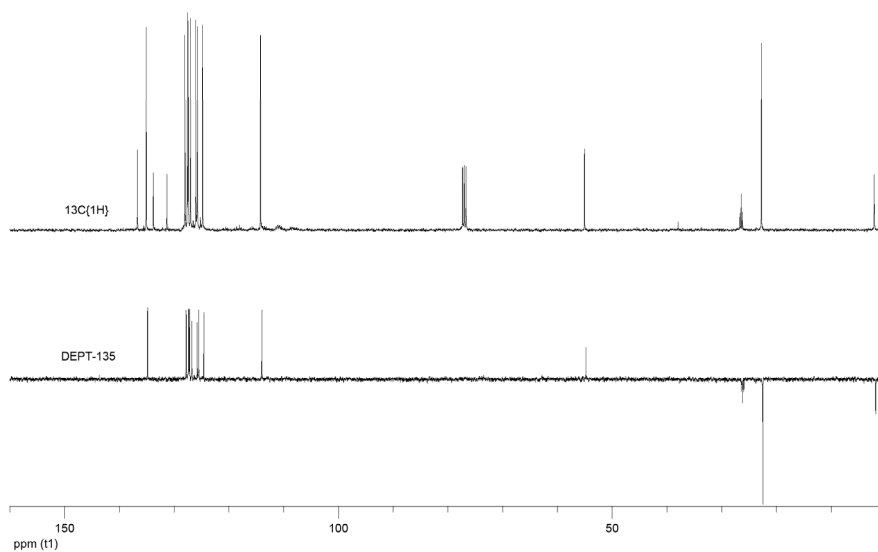
|                                                       |                                                                                                                          |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| <b>CBr<sub>4</sub></b>                                | sublimed immediately under vacuum 0.1 mmHg at 120 °C before use                                                          |
| <b>Cu(BF<sub>4</sub>)<sub>2</sub>.nH<sub>2</sub>O</b> | commercially supplied from Aldrich                                                                                       |
| <b>Cu(OTf)<sub>2</sub></b>                            | commercially supplied from Aldrich                                                                                       |
| <b>CuI</b>                                            | commercially supplied from Aldrich                                                                                       |
| <b>C<sub>8</sub>F<sub>17</sub>H<sub>4</sub>I</b>      | commercially supplied from Fluorochem                                                                                    |
| <b>C<sub>10</sub>F<sub>21</sub>H<sub>4</sub>I</b>     | commercially supplied from Fluorochem                                                                                    |
| <b>Dppp</b>                                           | commercially supplied from Acros                                                                                         |
| <b>GeCl<sub>4</sub></b>                               | commercially supplied from Aldrich                                                                                       |
| <b>Hypogel<sup>®</sup>-OH</b>                         | commercially supplied from Fluka                                                                                         |
| <b>NaI</b>                                            | commercially supplied from Lancaster                                                                                     |
| <b>NCS</b>                                            | rapidly re-crystallised from glacial acetic acid and wash with cold H <sub>2</sub> O followed by dried <i>in vacuo</i> . |
| <b>Pd(MeCN)<sub>2</sub>Cl<sub>2</sub></b>             | commercially supplied from Aldrich                                                                                       |
| <b>PPh<sub>3</sub></b>                                | commercially supplied from Aldrich                                                                                       |
| <b>P(2-Tol)<sub>3</sub></b>                           | commercially supplied from Acros                                                                                         |
| <b><i>Si</i>-propyl bromide</b>                       | commercially supplied from Crawford Scientific                                                                           |
| <b>TBAF.3H<sub>2</sub>O</b>                           | commercially supplied from Acros                                                                                         |

## Appendix 3: NMR spectra

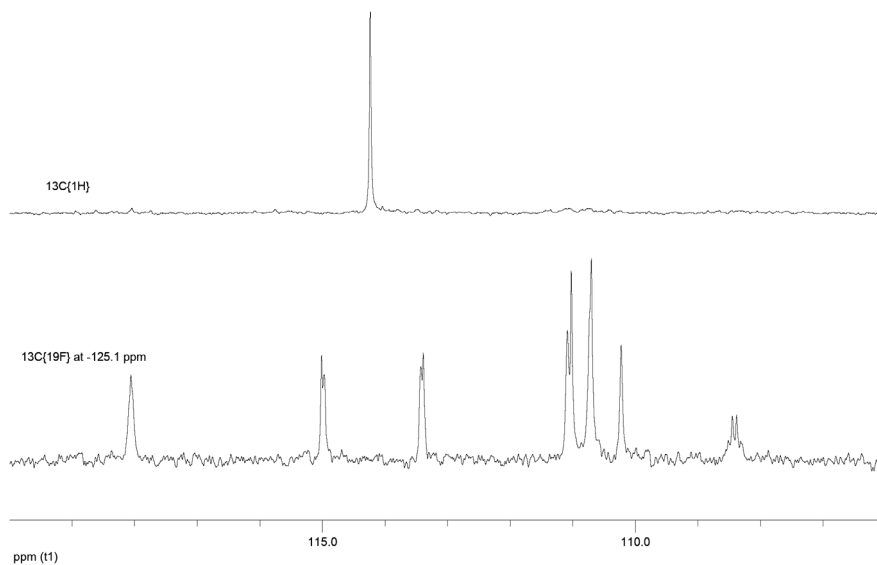
### A3.1 <sup>1</sup>H NMR of Rf-tagged arylgermane 6a (400 MHz, CDCl<sub>3</sub>)



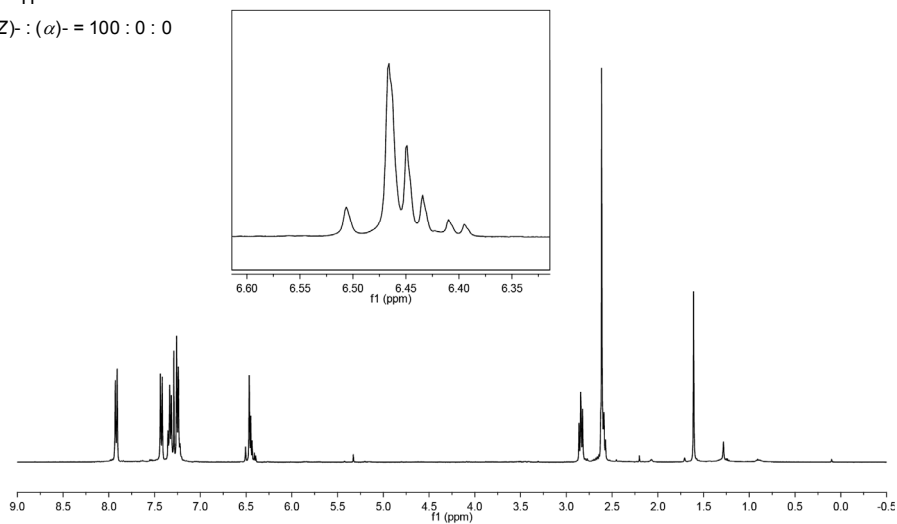
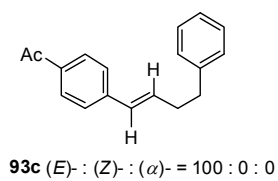
**A3.2  $^{13}\text{C}\{^1\text{H}\}$  and DEPT-135 NMR of  $^1\text{H}$  NMR of Rf-tagged arylgermane 6a**  
(100.7 MHz,  $\text{CDCl}_3$ )



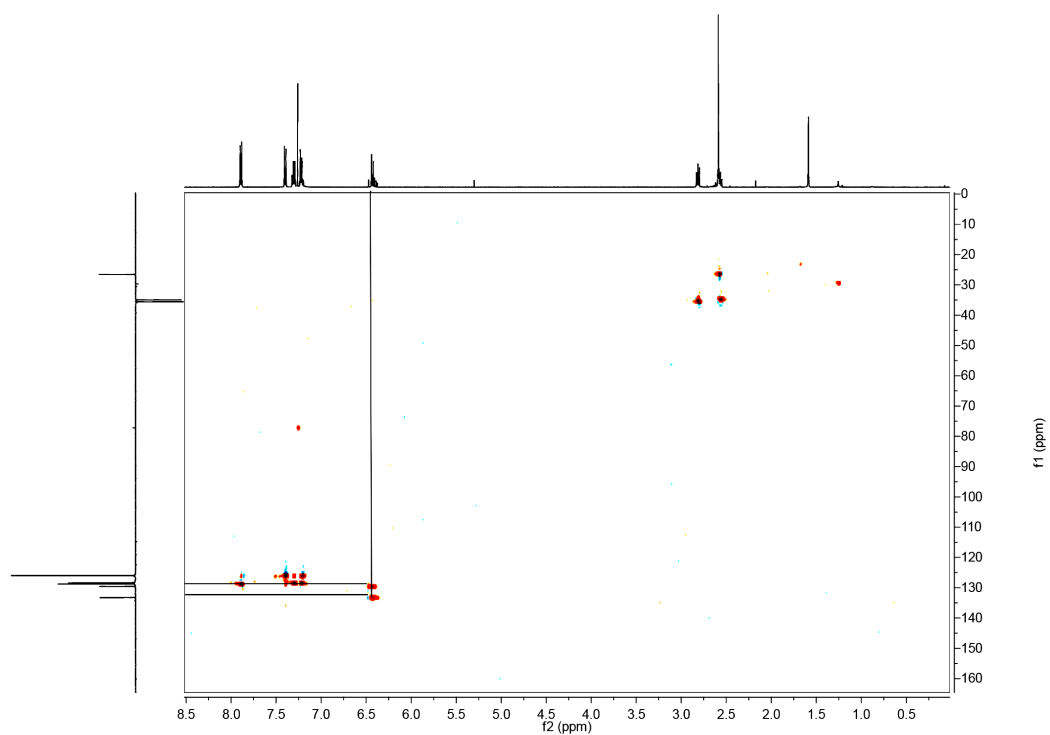
### A3.3 $^{13}\text{C}\{^{19}\text{F}\}$ decoupled NMR of Rf-tagged arylgermane **6a** (100.7 MHz, $\text{CDCl}_3$ )



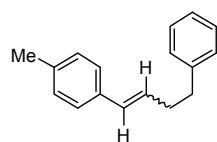
### A3.4 $^1\text{H}$ NMR of (*E*)-styrene **93c** (400 MHz, $\text{CDCl}_3$ )



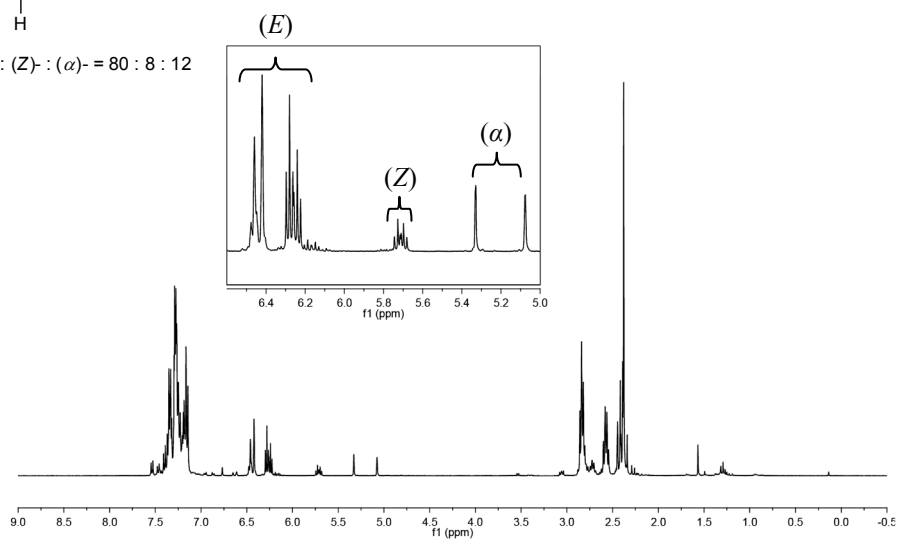
### A3.5 HSQC of (*E*)-styrene **93c** (500 MHz, CDCl<sub>3</sub>)



### A3.6 <sup>1</sup>H NMR of 1-(4-*para*-tolylbut-3-enyl)benzene **93e** (400 MHz, CDCl<sub>3</sub>)



**93e** (*E*)- : (*Z*)- : ( $\alpha$ )- = 80 : 8 : 12



## 5. References

- (1) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.
- (2) Mazur, S.; Jayalekshmy, P. *J. Am. Chem. Soc.* **1979**, *101*, 677-783.
- (3) Hiroshige, M.; Hauske, J. R.; Zhou, P. *J. Am. Chem. Soc.* **1995**, *117*, 11590-11591.
- (4) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discov.* **2002**, *1*, 573-586.
- (5) Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, P. J. *J. Chem. Soc., Perkin Trans. I* **1999**, 1251-1252.
- (6) Zhu, D.-W. *Synthesis* **1993**, 953-954.
- (7) Horváth, I. T.; Rabái, J. *Science* **1994**, *266*, 72-75.
- (8) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823-826.
- (9) Ubeda, M. A. *J. Chem. Edu.* **2006**, *83*, 84-92.
- (10) <http://www.fluorous.com/02primer.html#solid> (accessed Mar. 2009)
- (11) Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714-6715.
- (12) Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069-9072.
- (13) Zhang, W. *Tetrahedron* **2003**, *59*, 4475-4489.
- (14) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837-11865.
- (15) Zhang, W.; Lu, Y. *J. Comb. Chem.* **2006**, *8*, 890-896.
- (16) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH Verlag GmbH & Co., Weinheim, 2004.
- (17) Cheong, W. J.; Carr, P. W. *J. Liq. Chrom.* **1987**, *10*, 561-581.
- (18) Spivey, A. C.; Martin, L. J.; Tseng, C.-C.; Ellames, G. J.; Kohler, A. D. *Org. Biomol. Chem.* **2008**, *6*, 4093-4095.
- (19) Thomas, R. H. *The Chemistry of Natural Products*; Blackie and Son, Glasgow, 1985.
- (20) Tomlin, C. D. S. *The Pesticide Manual*; 12<sup>th</sup> ed.; British Crop Protection Council, Surrey, UK, 2006.
- (21) Kim, S.; Lee, J. W.; Kang, S. O.; Lo, J.-J.; Yum, J.-H.; Fantacci, S.; Angelis, F. D.; Censo, D. D.; Nazeeruddin, M. K.; Grtzel, M. *J. Am. Chem. Soc.* **2006**, *128*, 16701-16707.
- (22) Nuyken, O.; Jungermann, S.; Wiederhirn, V.; Bacher, E.; Meerholz, K. *Monatsh. Chem.* **2006**, *137*, 811-824.
- (23) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443-3447.
- (24) Whitty, A.; Kumaravel, G. *Nat. Chem. Biol.* **2006**, *2*, 112-118.
- (25) Spivey, A. C.; Arseniyadis, S.; Fekner, T.; Maddaford, A.; Leese, D. P. *Tetrahedron* **2006**, *62*, 295-301.

- (26) Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15-32.
- (27) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857-898.
- (28) Smrcina, M.; Lorence, M.; Hamus, V.; Kocovsky, P. *Synlett* **1991**, 231-232.
- (29) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.
- (30) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174-2185.
- (31) Lewin, A. H.; Cohen, T. *Tetrahedron Lett.* **1965**, *6*, 4531-4536.
- (32) Xi, M.; Bent, B. E. *J. Am. Chem. Soc.* **1003**, *115*, 7426-7433.
- (33) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577-2580.
- (34) Bjiirklund, C.; Nilsson, M. *Tetrahedron Lett.* **1966**, *7*, 675-678.
- (35) Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276-9282.
- (36) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662-664.
- (37) Gooßen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824-4833.
- (38) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297-2360.
- (39) Hattori, T.; Takeda, A.; Yamabe, O.; Miyano, S. *Tetrahedron* **2002**, *58*, 233-238.
- (40) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789-794.
- (41) Massound, T. F.; Gambhir, S. S. *Genes Dev.* **2003**, *17*, 545-580.
- (42) Willmann, J. K.; van Bruggen, N.; Dinkelborg, L. M.; Gambhir, S. S. *Nat. Rev. Drug Discov.* **2008**, *7*, 591-607.
- (43) Kuhl, D. E.; Ewaeds, R. Q. *Radiology* **1964**, *83*, 926-936.
- (44) Langner, J. MSc Thesis, University of Applied Sciences, Dresden, 2003.
- (45) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501-1516.
- (46) Lecomate, R. In *Nuclear Physics Methods and Accelerators in Biology and Medicine: Fourth International Summer School on Nuclear Physics Methods and Accelerators in Biology and Medicine*; Granja, C., Leroy, C., Stekl, I., Eds.; AIP Conference Proceedings: Prague, 2007; Vol. 958, p 115-122.
- (47) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.
- (48) Negish, E.-I. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons, Inc., New York, 2002.
- (49) Labadie, J. W.; Tueting, D.; Stille, S. K. *J. Org. Chem.* **1983**, *48*, 4634-4642.
- (50) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866-867.
- (51) Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340-348.
- (52) Hiyama, T.; Hatanaka, Y. *Pure. Appl. Chem.* **1994**, *66*, 1471-.
- (53) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395-401.

- (54) Sonogashira, K. *J. Organomet. Chem.* **2002**, 653, 46-49.
- (55) Heck, R. F. In *Org. React.* 1982; Vol. 27, p 345-390.
- (56) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, 42, 4087-4089.
- (57) Duncton, M. A. J.; Pattenden, G. J. *Chem. Soc., Perkin Trans. 1* **1999**, 1235-1246.
- (58) Espinet, P.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, 43, 4704-4734.
- (59) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, 11, 3009-3013.
- (60) Csákaia, Z.; Skoda-Földesa, R.; Kollár, L. *Inorg. Chim. Acta* **1999**, 286, 93-97.
- (61) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, 25, 508-524.
- (62) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, 120, 9722-9723.
- (63) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, 47, 6338-6361.
- (64) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, 108, 3033-3040.
- (65) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585-9595.
- (66) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, 58, 5434-5444.
- (67) Casares, J. A.; Coco, S.; Espinet, P.; Lin, Y.-S. *Organometallics* **1996**, 14, 3058-3067.
- (68) Casares, J. A.; Espinet, P.; Salas, G. *Chem. Eur. J.* **2002**, 8, 4843-4853.
- (69) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, 122, 11771-11782.
- (70) Casado, A. L.; Espinet, P.; Gallego, A. M.; Martinez-Ilarduya, J. M. *Chem. Commun.* **2001**, 339-340.
- (71) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, 125, 8704-8705.
- (72) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, 102, 4933-4941.
- (73) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, 129, 12003-12010.
- (74) Hartwig, J. F. *Inorg. Chem.* **2007**, 46, 1936-1947.
- (75) Marino, J. P.; Long, J. K. *J. Am. Chem. Soc.* **1988**, 110, 7917-7919.
- (76) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, 59, 5909-5911.
- (77) Casado, A. L.; Espinet, P. *Organometallics* **2003**, 22, 1305-1309.
- (78) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Chem. Eur. J.* **2005**, 11, 3294-3308.
- (79) Yoshida, J.-I.; Itami, K. *Chem. Rev.* **2002**, 102, 3693-3716.
- (80) Deshpande, M. S. *Tetrahedron Lett.* **1994**, 35, 5613-5614.
- (81) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, 117, 3306-3307.
- (82) Hernan, A. G.; Guillot, V.; Kuvshinov, A.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, 44, 8601-8603.
- (83) Carrera, N.; Gutierrez, E.; Benavente, R.; Villavieja, M. M.; Albeniz, A. C.;

- Espinet, P. *Chem. Eur. J.* **2008**, *14*, 10141-10148.
- (84) Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539-4541.
- (85) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918-920.
- (86) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495-1498.
- (87) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727-1747.
- (88) Diederich, F.; Stang, P. J. *Metal-catalyzed Cross-coupling Reactions*; Wiley-VCH, Weinheim, Germany, 1998.
- (89) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61-85.
- (90) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268-270.
- (91) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, 1711-1714.
- (92) Hatanaka, Y.; Goda, K.-I.; Okahara, Y.; Hiyama, T. *Tetrahedron* **1994**, *50*, 8301-8316.
- (93) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309-1310.
- (94) Denmark, S. E.; Chio, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821.
- (95) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491-2494.
- (96) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75-85.
- (97) Denmark, S. E.; Sweis, R. *Acc. Chem. Res.* **2002**, *35*, 835-846.
- (98) Itami, K.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 5600-5601.
- (99) Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, *31*, 138-139.
- (100) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342-5349.
- (101) Nakao, Y.; Oda, T.; Sahoo, A. K.; Hiyama, T. *J. Organomet. Chem.* **2003**, *687*, 570-573.
- (102) Murata, M.; Ohara, H.; Oiwa, R.; Watanabe, S.; Masuda, Y. *Synthesis* **2006**, 1771-1774.
- (103) Itami, K.; Mitsudo, K.; Yoshida, J.-I. *J. Org. Chem.* **1999**, *64*, 8709-8714.
- (104) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 11577-11585.
- (105) Hagiwara, E.; Gouda, K.-I.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439-442.
- (106) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299-301.
- (107) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486-1499.
- (108) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876-4882.
- (109) Homsí, F.; Nozaki, K.; Hiyama, T. *Tetrahedron Lett.* **2000**, *41*, 5869-5872.
- (110) Homsí, F.; Hosoi, K.; Nozaki, K.; Hiyama, T. *J. Organomet. Chem.* **2001**, *624*, 208-216.

- (111) Asai, K.; Miracle, C. *Organic Germanium*; Japan Publications Inc., Tokyo, 1980.
- (112) Goodman, S. *Medical Hypotheses* **1988**, *26*, 207-215.
- (113) Wenger, G. R.; McMillan, D. E.; Chang, L. W. *Neurobehav. Toxicol. Teratol.* **1986**, *8*, 659-665.
- (114) Patai, S. *The Chemistry of Organic Germanium, Tin and Lead Compounds*; John Wiley & Sons Ltd., Chichester, England, 1995.
- (115) Huang, G.; Bai, Z.; Dai, S.; Xie, Q. *Appl. Organomet. Chem.* **1993**, *7*, 373.
- (116) Huheey, J. E.; Huheey, C. L. *J. Chem. Ed.* **1972**, *49*, 227-230.
- (117) Ikenaga, K.; Matsumoto, S.; Kikukawa, K. *Chem. Lett.* **1990**, *19*, 185-188.
- (118) Kosugi, M.; Tanji, T.; Tanaka, Y.; Yoshida, A.; Fugami, K.; Kameyama, M.; Migita, T. *J. Organomet. Chem.* **1996**, *508*, 255-257.
- (119) Nakamura, T.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3165-3167.
- (120) Gripton, C. J. G. PhD Thesis, University of Sheffield, 2004.
- (121) Hannah, J. PhD Thesis, Imperial College London, 2006.
- (122) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P.; Tseng, C. C.; Fraine, P. D.; Parr, N. J.; Scicinski, J. J. *Appl. Organomet. Chem.* **2007**, *21*, 572-589.
- (123) <http://www.msscientific.de/hpk125wlamp.htm> (assessed Mar. 2009)
- (124) Horspool, W. *Organic Photochemistry: A Comprehensive Treatment*; Ellis Horwood Limited, Chichester, England, 1992.
- (125) Fleming, S. A.; Jesen, A. W. *J. Org. Chem.* **1993**, *58*, 7135-7137.
- (126) Fleming, S. A.; Jesen, A. W. *J. Org. Chem.* **1996**, *61*, 7040-7044.
- (127) Zimmerman, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 8988-8991.
- (128) Mizuno, K.; Yahueda, M.; Otsuji, Y. *Chem. Lett.* **1988**, 229-232.
- (129) Tamao, K. *Adv. Silicon. Chem.* **1996**, *3*, 1-62.
- (130) Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270-280.
- (131) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 520-554.
- (132) Poremba, P.; Bruser, W.; Edelmann, F. T. *J. Fluorine Chem.* **1997**, *82*, 43-46.
- (133) Svec, P.; Padelkova, Z.; Cernosek, Z.; Proft, F. D.; Ruzicka, A. *J. Organomet. Chem.* **2008**, *693*, 2937-2941.
- (134) Li, J.-H.; Deng, C.-L.; Xie, Y.-X. *Synthesis* **2006**, 969-974.
- (135) Spivey, A. C.; Tseng, C. C.; Hannah, J. P.; Gripton, C. J. G.; Fraine, P. D.; Parr, N. J.; Scicinski, J. J. *Chem. Commun.* **2007**, 2926-2928.
- (136) Ernst, A.; Gobbi, L.; Vasella, A. *Tetrahedron Lett.* **1996**, *37*, 7959-7962.
- (137) Turner, D. PhD Thesis, University of Sheffield, 2004.
- (138) Turner, D. J.; Anemian, R.; Mackie, P. R.; Cupertino, D. C.; Yeates, S. G.;

- Turner, M. L.; Spivey, A. C. *Org. Biomol. Chem.* **2007**, *5*, 1752-1763.
- (139) BDiBlasi, C. M.; Macks, D. E.; Tan, D. S. *Org. Lett.* **2005**, 1777-1780.
- (140) Murray, P. J.; Kay, C.; Scicinski, J. J.; McKeown, S. C.; Watson, S. P.; Carr, R. A. E. *Tetrahedron Lett.* **1999**, 5609-5612.
- (141) Wagner, O.; Eicken, K.; Ammermann, E.; Lorenz, G.; Strathmann, S.; Koehle, H.; Retzlaff, G.; DE19615977A1; BASF.
- (142) Matheron, M. E.; Porchas, M. *Plant Dis.* **2004**, *88*, 665-668.
- (143) Cecchini, G. *Annu. Rev. Biochem.* **2003**, *72*, 77-109.
- (144) Hellwinkel, D.; Lammerzahn, F.; Hofmann, G. *Chem. Ber.* **1983**, 3375-3405.
- (145) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Elsevier, Oxford, 2002.
- (146) Mulhern, T. A.; Davis, M.; Thomas, J. A. *J. Org. Chem.* **1993**, *58*, 5537-5540.
- (147) Varasi, M.; Torre, A. D.; Heidempergher, F.; Pevarello, P.; Speciale, C.; Guidetti, I. P.; Wells, D. R.; Schwarcz, R. *Eur. J. Med. Chem.* **1996**, *31*, 11-21.
- (148) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, 1132-1136.
- (149) Cho, I.-S.; Gong, L.; Muchowski, J. M. *J. Org. Chem.* **1991**, *56*, 7288-7291.
- (150) Starling, S. M.; Vonwiller, S. C. *Tetrahedron Lett.* **1997**, *38*, 2159-2162.
- (151) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron Asymm.* **2004**, 3011-3013.
- (152) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1997**, *119*, 311-325.
- (153) Tapolcsanyi, P.; Maes, B. U. W.; Monsieurs, K.; Lemiere, G. L. F.; Riedl, Z.; Hajos, G.; Driessche, B. V.; Dommissie, R. A.; Matyus, P. *Tetrahedron* **2003**, *59*, 5919-5926.
- (154) Pyne, S. G. *Tetrahedron Lett.* **1987**, *28*, 4737-4740.
- (155) Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767-3776.
- (156) Noban, C. PhD Thesis, Imperial College London, 2006.
- (157) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1276-1279.
- (158) Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358-8359.
- (159) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33-41.
- (160) Marcial, M.-M.; Montserrant, P.; Roser, P. *J. Org. Chem.* **1996**, *61*, 2346-2351.
- (161) Parrish, J. P.; Flander, V. L.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2001**, *42*, 7729-7731.
- (162) Ehrenfreund, J.; Lamberth, C.; Tobler, H.; Walter, H.; WO 2004/058723.
- (163) Menchi, G.; Scrivanti, A.; Matteoli, U. *J. Mol. Catal. A* **2000**, *152*, 77-82.
- (164) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418 - 3420.
- (165) Boss, C.; Keese, R. *Tetrahedron* **1997**, *53*, 3111-3122.
- (166) Feldman, K. S.; Mareska, D. A. *J. Org. Chem.* **1999**, *64*, 5650-5660.

- (167) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286.
- (168) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466-468.
- (169) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084-14085.
- (170) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853-887.
- (171) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257-3282.
- (172) Marciniak, B. *Silicon Chem.* **2002**, *1*, 155-175.
- (173) Faller, J. W.; Kultyshev, R. G. *Organometallics* **2003**, *22*, 199-202.
- (174) Lukevics, E.; Arsenyan, P.; Belyakov, S.; Popelis, J. *J. Organomet. Chem.* **1998**, *558*, 155-161.
- (175) Wada, F.; Seiji, A.; Yonemaru, N.; Kikukawa, K.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1701-1703.
- (176) Esteruelas, M. A.; Martin, M.; Oro, L. A. *Organometallics* **1999**, *18*, 2267-2270.
- (177) Schwier, T.; Gevorgyan, V. *Org. Lett.* **2005**, *7*, 5191-5194.
- (178) Li, M. MSci Project Thesis, Imperial College London, 2009.
- (179) Han, X.-J.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.
- (180) Ikenaga, K.; Kikukawa, K.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1959-1964.
- (181) Hatanaka, Y.; Hiyama, T. *J. Organomet. Chem.* **1994**, *465*, 97-100.
- (182) Kikukawa, K.; Umekawa, H.; Matsuda, T. *J. Organomet. Chem.* **1986**, *311*, C44-C46.
- (183) Farina, V.; Hossain, M. A. *Tetrahedron Lett.* **1996**, *37*, 6997-7000.
- (184) Alvisi, D.; Blart, E.; Bonini, B. F.; Mazzanti, G.; Ricci, A.; Zani, P. *J. Org. Chem.* **1996**, *61*, 7139-7146.
- (185) Flohr, A. *Tetrahedron Lett.* **1998**, *39*, 5177-5180.
- (186) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146-151.
- (187) Busacca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Musza, L.; Rodger, C. A. *J. Org. Chem.* **1994**, *59*, 7553-7556.
- (188) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2004**, *43*, 3928-3932.
- (189) Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol. Rev.* **2002**, *54*, 161-202.
- (190) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561-564.
- (191) Gerard, C. M.; Mollreau, C.; Vassart, G.; Parmentier, M. *Biochem. J.* **1991**, *279*, 129-134.

- (192) Shire, D.; Calandra, B.; Delpech, M.; Dumont, X.; Kaghad, M.; Fur, L. G.; Caput, D.; Ferrara, P. *J. Biol. Chem.* **1996**, *271*, 6941-6946.
- (193) Howlett, A. C. *Brit. J. Pharmacol.* **2004**, *142*, 1209-1218.
- (194) Pagotto, U.; Marsicano, G.; Cota, D.; Lutz, B.; Pasquali, R. *Endocr. Rev.* **2006**, *27*, 73-100.
- (195) Di Marzo, V.; Goparaju, S. K.; Wang, L.; Liu, J.; Batkai, S.; Jarai, Z.; Fezza, F.; Miura, G. I.; Palmiter, R. D.; Sugiura, T.; Kunos, G. *Nature* **2001**, *410*, 822-825.
- (196) Rinaldi-Carmona, M.; Barth, F.; Hkaulme, M.; Shireb, D.; Calandrab, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G.; Caputb, D.; Ferrarab, P.; Soubrie, P.; Brelike, J. C.; Fura, G. L. *FEBS Lett.* **1994**, *350*, 240-244.
- (197) Stoit, A. R.; Lange, J. H. M.; den Hartog, A. P.; Ronken, E.; Tipker, K.; van Stuivenberg, H. H.; Dijkman, J. A. R.; Wals, H. C.; Kruse, C. G. *Chem. Pharm. Bull.* **2002**, *50*, 1109-1113.
- (198) Murineddu, G.; Ruiiu, S.; Loriga, G.; Manca, I.; Lazzari, P.; Reali, R.; Pani, L.; Toma, L.; Pinna, G. A. *J. Med. Chem.* **2005**, *48*, 7351-7362.
- (199) Jones, D. *Nat. Rev. Drug Discov.* **2008**, *7*, 961-962.
- (200) Strange, P. G. *Trends Pharmacol. Sci.* **2002**, *23*, 89-95.
- (201) Pertwee, R. G. *Life Sci.* **2005**, *76*, 1307-1324.
- (202) Kenakin, T. *Trends Pharmacol. Sci.* **2004**, *25*, 186-192.
- (203) Lange, J. H. M.; Kruse, C. G. *Drug Discov. Today* **2005**, *10*, 693-702.
- (204) Thomas, B.; Zhang, Y.; Brackeen, M.; Page, K.; Mascarella, S.; Seltzman, H. *AAPS J.* **2006**, *8*, E665-E671.
- (205) Hurst, D. P.; Lynch, D. L.; Barnett-Norris, J.; Hyatt, S.; Seltzman, H.; Zhong, M.; Song, Z.-H.; Nie, J.-J.; Lewis, D.; Reggio, P. H. *Mol. Pharmacol.* **2002**, *62*, 1274-1287.
- (206) Mathews, W. B.; Scheffel, U.; Finley, P.; Ravert, H. T.; Frank, R. A.; Rinaldi-Carmona, M.; Barth, F.; Dannals, R. F. *Nucl. Med. Biol.* **2000**, *27*, 757-762.
- (207) Mathews, W. B.; Scheffel, U.; Rauseo, P. A.; Ravert, H. T.; Frank, R. A.; Ellames, G. J.; Herbert, J. M.; Barth, F.; Rinaldi-Carmona, M.; Dannals, R. F. *Nucl. Med. Biol.* **2002**, *29*, 671-677.
- (208) Lia, Z.; Gifforda, A.; Liub, Q.; Thotapallyb, R.; Dinga, Y.-S.; Makriyannisb, A.; Gatley, S. J. *Nucl. Med. Biol.* **2005**, *32*, 361-366.
- (209) Lan, R.; Fan, P.; Gatley, S. J.; Volkow, N. D.; Fernado, S. R.; Pertwee, R.; Makriyannis, A. *AAPS Pharmsci* **1999**, *1*, article 4.
- (210) Berdinga, G.; Schneiderb, U.; Gielowa, P.; Buchertc, R.; Donnerstagd, F.; Brandae, W.; Knappa, W. H.; Emrichb, H. M.; Müller-Vahlb, K. *Psychiat.*

- Res.-Neuroim.* **2006**, *147*, 249-256.
- (211) Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769-776.
- (212) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.-J.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183-190.
- (213) Eaborn, C.; Pande, K. C. *J. Chem. Soc.* **1960**, 1566-1571.
- (214) Jones, T. C. Ph.D Thesis, University of Sherfield, 2004.
- (215) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845.
- (216) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215-4217.
- (217) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, 2481-2483.
- (218) Armstrong, A.; Brackenridge, I.; Jackson, R. P. W.; Rirk, J. M. *Tetrahedron Lett.* **1988**, 2483-2486.
- (219) Amos, R. I. J.; Corulay, B. S.; Schiesser, C. H.; Smith, J. A.; Yates, B. F. *Chem. Commun.* **2008**, 1695-1697.
- (220) Gatley, S. J.; Gifford, A. N.; Volkow, N. D.; Lan, R.; Makriyannis, A. *Eur. J. Pharmacol.* **1996**, *307*, 331-338.
- (221) Lan, R.; Gatley, S. J.; Makriyannis, A. *J. Labelled. Compd. Rad.* **1996**, *38*, 875-881.
- (222) Mohanakrishnan, A.; Prakash, C.; Ramesh, N. *Tetrahedron* **2006**, *62*, 3242-3247.
- (223) Krishna Mohan, K. V.; Narrender, N.; Kulkarni, S. J. *Tetrahedron Lett.* **2004**, *45*, 8015-8018.
- (224) Wilson, S. R.; Jacob, L. A. *J. Org. Chem.* **1986**, *51*, 4833-4836.
- (225) Sha, C.-K.; Young, J.-J.; Jean, T.-S. M. *J. Org. Chem.* **1987**, *52*, 3919-3920.
- (226) Moerlein, S. M. *J. Org. Chem.* **1987**, *52*, 664-667.
- (227) Arstan, E.; Hoff, P.; Skattebol, L.; Skretting, A.; Breistol, K. *J. Med. Chem.* **2003**, *46*, 3021-3032.
- (228) MacDonald, A. A.; Dewitt, S. H.; Ghosh, S.; Hogan, E. M.; Kieras, L.; Czarnik, A. W.; Ramage, R. *Mol. Divers.* **1995**, *1*, 183-186.
- (229) Sucholeiki, I. *Mol. Divers.* **1999**, *4*, 25-30.
- (230) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2924.
- (231) Spivey, A. C.; Diaper, C. M.; Adams, H.; Rudge, A. J. *J. Org. Chem.* **2000**, *65*, 5253-5263.
- (232) Shimda, S.; Yamazaki, O.; Tanaka, T.; Rao, M. L. N.; Suzuki, Y.; Tanaka, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1845-1848.
- (233) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447-3452.

- (234) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Zhen, Y. *Org. Lett.* **2004**, *6*, 221-224.
- (235) Uozumi, Y.; Yasuhiro *Organic letters* **2002**, *4*, 2997.
- (236) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364-9370.
- (237) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236-5243.
- (238) Kataoka, N.; Noriyasu *Journal of organic chemistry* **2002**, *67*, 5553.
- (239) Cella, R.; Cunha, R. L. O. R.; Reis, A. E. S.; Pimenta, D. C.; Klitzke, C. F.; Stefani, H. A. *J. Org. Chem.* **2006**, *71*, 244-250.
- (240) Liu, L.; Zhang, Y. Y.; Xin, B. *J. Org. Chem.* **2006**, *71*, 3994-3997.
- (241) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802 - 1808.
- (242) Christensen, S. B.; Karpinski, J. M.; Ryan, M. D.; Bender, P. E.; US5977122(A); SmithKline Beecham.
- (243) Miyake, Y.; Wu, M.; Rahman, M. J.; Kuwatani, Y.; Iyoda, M. *J. Org. Chem.* **2006**, *71*, 6110 - 6117.
- (244) Bradsher, C. K.; Wissow, L. J. *J. Am. Chem. Soc.* **1946**, *68*, 404-405.
- (245) Bejot, R.; Anjaiah, S.; Falck, J. R.; Mioskowski, C. *Eur. J. Org. Chem.* **2007**, 101-107.
- (246) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002**, *43*, 2191-2194.
- (247) Mu, B.; Li, T.; Xu, W.; Zeng, G.; Liu, P.; Wu, Y. *Tetrahedron* **2007**, *63*, 11475-11488.
- (248) Alacid, E.; Najera, C. *J. Org. Chem.* **2008**, *73*, 2315-2322.
- (249) Hupe, E.; Calaza, M. I.; Knoche, P. *Chem. Commun.* **2002**, 1390-1391.
- (250) Alekseeva, O. O.; Mahadevan, A.; Wiley, J. L.; Martin, B. R.; Razdan, R. K. *Tetrahedron Lett.* **2005**, *46*, 2159-2161.
- (251) Makriyannis, A.; Liu, Q.; Thotapally, R.; US20060100208A1.
- (252) Ehrlich, F.; Pistchimuka, P. *Chem. Ber.* **1912**, *45*, 2428.