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A new germanium based linker for solid phase synthesis of aromatic compounds

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An efficient three-step synthesis of germyl linker precursor 4 is described which enables a simple two step immobilisation of lithiated aromatics to Argogel™ polymer; cleavage from the polymer support *via ipso*-degermylation with TFA, ICl, Br_2 and NCS provides protio-, iodo-, bromo- and chloroaryls, respectively.

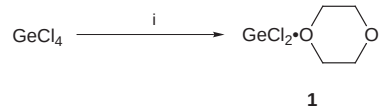
The development of new linkers for the immobilisation of organic compounds on functionalised polymer supports is an area of current interest.[1] The immobilisation of aromatics has commanded particular importance as compounds of this type are pervasive constituents of pharmaceuticals. Protecting-group linker strategies are suitable for this purpose provided that the functional group unmasked on cleavage is required in the target molecules. If not, then a traceless linker (*e.g.* arylsilane based) can be employed.[2] Arylsilane cleavage is generally achieved *via* acidolytic or basic fluoridolytic *ipso*-protodesilylation,[3] or by electrophilic *ipso*-halodesilylation using Br_2 or ICl to release aryl bromides and iodides respectively.[4] The ability to employ a range of electrophiles for cleavage is desirable for library preparation as diversity is introduced on release into solution.

We were interested in devising a new aryl linker susceptible to cleavage by an increased range of electrophiles and to this end the work of Vasella[5] on trimethylgermane protection of alkynes drew our attention. Vasella has noted that relative to the corresponding alkynylsilanes, alkynylgermanes are more readily cleaved by electrophiles (due to the more powerful β-effect of germanium)[6] and additionally display enhanced stability towards bases and nucleophiles. These properties combined with the low toxicity of aryl- and alkylgermane compounds suggested to us that an arylgermane-based linker might provide a useful addition to the current repertoire of traceless linkers.

During the course of our studies Ellman,[7] in response to the low reactivity of an electron deficient arylsilane bound benzodiazepine library towards acidolytic cleavage, reported the first arylgermane linker. Ellman demonstrated that his arylgermane linker was more readily cleaved by electrophiles (TFA, Br_2) than the corresponding arylsilane linker and that his linker was compatible with a range of transformations associated with the introduction and manipulation of a diverse array of functional groups. In the light of this pioneering 'proof of concept' our efforts focussed on the development of a more economic arylgermane linker as Ellman's linker synthesis relied on Me_2GeCl_2 for introduction of the germanium. This compound is expensive and is difficult to prepare from $GeCl_4$ (the cheapest commercial source of germanium).

One interesting facet of germanium chemistry is the coordination and insertion reactions associated with dihalogermylenes.[8] We opted to exploit this chemistry in the preparation of our arylgermane linker. Thus, known dichlorogermylene–1,4-dioxane complex, $GeCl_2.C_4H_8O_2$ **1**, was synthesised in one step from $GeCl_4$ by reduction with tetramethyldisiloxane (TMDS) in refluxing dioxane (Scheme 1). This reaction routinely provides 70–90% isolated yields of this stable crystalline complex on a preparative scale.[9]

Various dichlorogermylene complexes have been reported to undergo thermally induced insertion into C–Cl bonds.[10] We found that the dioxane complex **1** inserts cleanly into the homobenzylic C–Cl bond of 4-(2-chloroethyl)phenol **2**.† Simply heating the two components in a Carius tube with a minimum amount of dioxane furnished trichlorogermane **3** in 91% yield. Exhaustive methylation by refluxing with an excess of MeMgBr then furnished trimethylgermane linker precursor **4**‡ in 82% yield[11] (Scheme 2).



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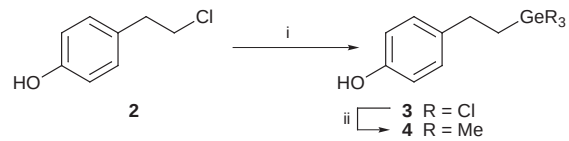
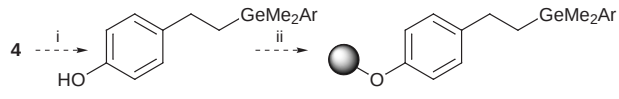
Scheme 1 *Reagents and conditions*: i, TMDS, 1,4-dioxane, 3 h, 100 °C.



Scheme 2 *Reagents and conditions*: i, $GeCl_2.C_4H_8O_2$ **1**, 1,4-dioxane, 16 h, 140 °C (91%); ii, MeMgBr, Et_2O, toluene, 16 h, 110 °C (82%).

We envisaged that immobilisation of an aromatic compound onto a hydroxy functionalised polymer support could be achieved in a simple two step procedure using trimethylgermane linker precursor **4**. This would involve selective monohalodemethylation and *in situ* arylation with the appropriate aryl organometallic species (→ **I**, Scheme 3) followed by Mitsunobu coupling of the resulting phenolic dimethylarylgermane to the polymer support (→ **II**, Scheme 3).



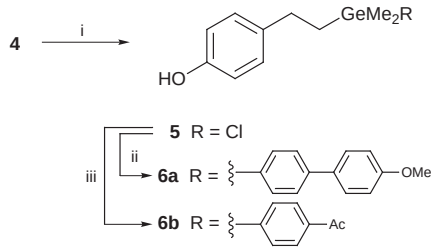
I **II**

Scheme 3 Two step immobilisation strategy: i, mono-halodemethylation and *in situ* arylation with aryl organometallic; ii, Mitsunobu coupling to resin.

To exemplify this protocol we report here the immobilisation of two aromatic systems: 4-(4′-methoxy)biphenyl and 4-acetophenone. The former was chosen as this biphenyl would provide a stringent test system on which to assess electrophilic cleavage by virtue of having an electron rich aryl group susceptible itself to competitive electrophilic aromatic substitution. The latter was chosen as acetophenone provides a versatile functional handle for library construction.

Butyltrimethylgermane (Me_3BuGe) has been shown to undergo selective mono-chlorodemethylation to give chlorobutyldimethylgermane ($Me_2BuGeCl$) upon treatment with $SnCl_4$.[12] We were able to replicate this exquisite chemoselectivity with our linker precursor **4**. Thus treatment with $SnCl_4$ in $MeNO_2$ gave chlorodimethylgermane **5** quantitatively (Scheme 4).

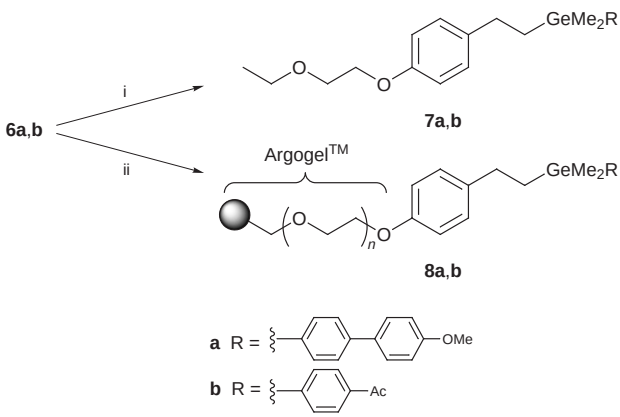
Arylation of **5** was accomplished by refluxing overnight in toluene–THF with the appropriate aryllithium reagent.[13] The 4-litho-4′methoxybiphenyl and dioxolane protected 4-lithioacetophenone, used to prepare arylgermanes **6a** and **6b**



Scheme 4 *Reagents and conditions*: i, $SnCl_4$, $MeNO_2$, 16 h, 50 °C (100%); ii, 4-bromo-4′-methoxybiphenyl, BuLi, hexane, THF, toluene, 16 h, 110 °C [**6a** (82%)]; iii, (a) 2-(4-bromophenyl)-2-methyl-1,3-dioxolane, BuLi, THF, toluene, 16 h, 110 °C, (b) PPTS, acetone, H_2O, 48 h, 67 °C [**6b** (84% from **5**)].

respectively, were made from the corresponding bromides by standard lithium–halogen exchange at −78 °C. Dioxolane deprotection was accomplished using PPTS in acetone–H_2O (Scheme 4).

Tsunoda's modified Mitsunobu redox system of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)–PBu_3 was found to effect efficient coupling of arylgermanes **6a** and **6b** to ethoxyethanol to give model systems **7a** and **7b** respectively.[14] Ethoxyethanol was selected as a solution phase 'surrogate' for PEG based Argogel™.§ Use of a solution phase model for development of appropriate Mitsunobu coupling conditions was vindicated when these optimised conditions were employed without modification for the efficient loading of arylgermanes **6a** and **6b** to Argogel™. Thus following successive washing of the polymer with DMF, EtOH, THF, Et_2O and CH_2Cl_2 the aryl functionalised polymers **8a** and **8b** were obtained with loading levels of 0.47 and 0.43 mmol g^{-1}¶ respectively (Scheme 5).



Scheme 5 *Reagents and conditions*: i, $EtOCH_2CH_2OH$, TMAD, PBu_3, PhH, room temp. 16 h [**7a** (98%), **7b** (87%)]; ii, Argogel™, TMAD, PBu_3, PhH, room temp., 16 h (**8a**, **8b**, see text).

Electrophilic cleavage conditions were optimised initially using solution phase biarylgermane model system **7a**. It was pleasing to find that treatment with TFA, ICl and Br_2 at room temperature led to quantitative cleavage of the aryl–germanium bond, yielding the protio-, iodo- and bromobiaryl products **9**, **10** and **11** respectively. Furthermore, chlorobiaryl **12** could also be obtained cleanly using NCS (or Dichloramine-T) in refluxing THF. There were no traces of products resulting from competitive electrophilic substitution in the anisole ring. Minimal optimisation was required to translate this success to cleavage from Argogel™. Thus when employing functionalised resin **8a**, monitoring release of the biaryl products into solution by analytical HPLC of the *crude* washings revealed all these protocols to proceed cleanly and quantitatively (Fig. 1). The identity of the released biaryls **9**, **10**, **11** and **12** were confirmed in each case by co-injection with authentic samples.

To conclude, we have developed an efficient three step synthesis of germyl linker precursor **4** (from inexpensive $GeCl_4$) and demonstrated that this compound can be employed in a simple two step immobilisation of lithiated aromatics to Argogel™ polymer. Clean release from the polymer by electrophilic *ipso*-degermylation affords either protio-, iodo-, bromo- or chloroaryls, depending on the electrophile employed.

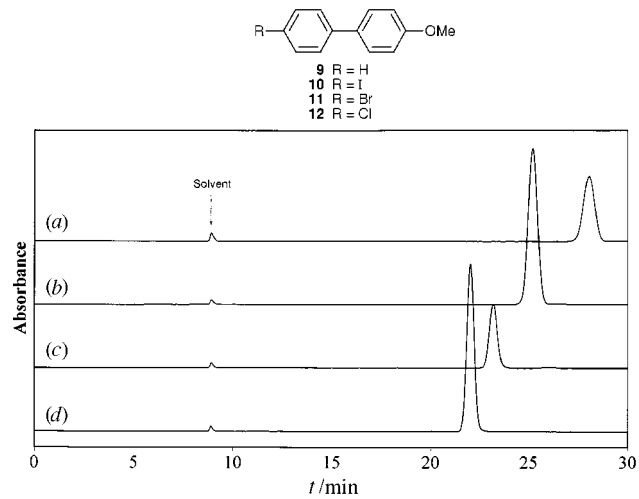


Fig. 1 HPLC traces of biaryls cleaved from Argogel™. [Column: Hichrom spherisorb-S5W (25 × 0.8 cm), eluting with 80 : 20 hexane–$CHCl_3$, 1.0 ml min^{-1}]. *Reagents and conditions*: (*a*) TFA room temp., 16 h (→ **9**); (*b*) ICl, CH_2Cl_2, room temp., 30 min (→ **10**); (*c*) NCS, THF, 67 °C, 14 h (→ **12**); (*d*) Br_2, CH_2Cl_2, room temp., 2 h (→ **11**).

We are currently preparing a library of aryl containing compounds using functionalised polymer **8b** and extending the range of electrophiles able to effect cleavage of the aryl–germanium bond.

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Notes and references

† 4-(2-Chloroethyl)phenol is readily prepared in 90% yield from commercially available 4-(2-hydroxyethyl)phenol by heating in concentrated HCl (ref. 15).

‡ Now commercially available from AFChemPharm Ltd., Unit B31-14, Manor Development Centre, 40 Alison Crescent, Sheffield, UK S2 1AS.

§ Commercial Argogel™ (nominal loading level 0.49 mmol g^{-1}) was selected as the polymer support due to its non-benzylic hydroxy functionalisation and favourable characteristics for high resolution MAS ^1H NMR.

¶ As determined by mass balance (of introduction and subsequent cleavage). Polymers **8a** and **8b** were also characterised by solid state MAS ^1H NMR.

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