A strategy for isotope containment during radiosynthesis—devolatilisation of bromobenzene by fluorous-tagging–Ir-catalysed borylation *en route* to the 4-phenylpiperidine pharmacophore†

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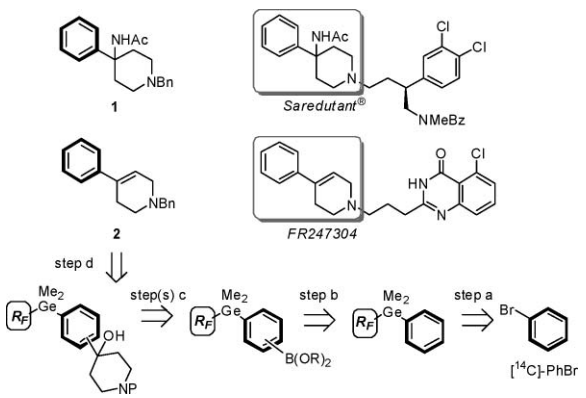
Syntheses of two 4-phenylpiperidines from bromobenzene have been developed involving anchoring to a fluorous-tag, Ir-catalysed borylation, Pd- and Co-catalysed elaboration then traceless cleavage. Although performed using 'cold' (*i.e.* unlabelled) bromobenzene as the starting material, these routes have been designed to minimise material loss *via* volatile intermediates and expedite purification during radiosynthesis from 'hot' (*i.e.* [^{14}C] labelled) bromobenzene.

[^{14}C]-Labelled compounds are used widely in pharmaceutical development for absorption, distribution, metabolism and elimination (ADME) studies.[1] Their synthesis is uniquely challenging because only a limited set of simple [^{14}C]-labelled starting materials are available (*e.g.* barium carbonate, potassium cyanide, bromobenzene) and these isotopically enriched intermediates are toxic and require rigorous containment. Issues of containment extend acutely to the first steps in a synthesis which often proceed *via* low molecular weight volatile synthetic intermediates. 'Anchoring' the labelled precursor to a fluorous phase-tag[2] *via* a traceless linker would solve this problem by rendering the labelled material involatile during subsequent transformations whilst also greatly aiding purification during elaboration and allowing for facile phase-tag removal once sufficient mass to ensure involatility had been attained. This would benefit the radiochemist by minimising inhaled radiation and the environment by reducing radioactive fume-hood exhaust. That only a limited set of building blocks are used routinely by radiochemists is also advantageous for developing generic protocols to realise these benefits. Here we provide proof-of-concept for this tactic by the development of a method for traceless anchoring and then CH activation of bromobenzene. All the chemistry described has thus far been carried out only using cold (*i.e.* unlabelled) bromobenzene.

[^{14}C]-Bromobenzene is widely used as a starting material for the preparation of radiolabelled drugs for ADME studies because aryl rings are pervasive components of drug substances and generally undergo minimal metabolic degradation. Its introduction into biaryl, styrenyl and phenyl ketone pharmacophores is generally accomplished *via* Pd-catalysed transformations; either directly as the electrophilic component [*via* Pd(0) oxidative addition] or as the nucleophilic component by prior conversion to the phenyl boronic acid/ester.[3] The choice of role is usually dictated by the electronic requirements and/or availability of the coupling partner. Isotopic containment is particularly problematic in the latter role due to the formation of labelled benzene as a volatile by-product of *in situ* deboronation.[4]

We envisaged a simple and potentially widely applicable strategy to circumvent this problem and illustrate here its utility for the preparation of two key derivatives of the 'privileged'[5] 4-phenypiperidine pharmacophore: acetylaminopiperidine **1** and tetrahydropyridine **2**.‡ These motifs are found in many drugs, particularly various neuro-active agents such as neurokinin (NK) receptor antagonists [*e.g.* Saredutant®, in development for depression][6] and poly(ADP-ribose) polymerase (PARP) inhibitors (*e.g.* FR247304, in development for stroke)[7] (Scheme 1).



Scheme 1 4-Phenylpiperidine based pharmacophores **1** and **2**, as found in Saredutant® and FR247304, and retrosynthetic strategy for their phase-tagged synthesis from [^{14}C]-bromobenzene.

The three key generic steps in this strategy are the initial anchoring to the fluorous-tag (step a), the CH activation–functionalisation (step b), and the traceless–functionalisative cleavage (step d) with the intervening mass-enhancing elaboration steps for target intermediates **1** and **2** being Suzuki and hydration reactions (steps c, Scheme 1).

Step a was envisaged to be the reaction between phenyllithium (from bromobenzene *via* bromine–lithium exchange) and a germyl bromide functionalised fluorous phase-tag. Although this reaction has the potential for loss of labelled benzene when performed on hot (*i.e.* [^{14}C]labelled) bromobenzene, loss here is non-critical as this step is necessarily performed on a vacuum line that affords full containment from the commercially supplied ampoule. This reaction was however anticipated to be high yielding and the

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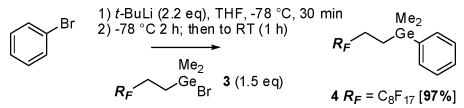
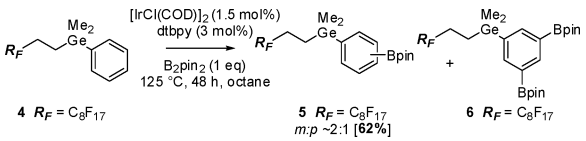
resulting C–Ge anchoring bond was expected to be robust to a wide range of subsequent chemical manipulations[8] whilst still allowing for traceless cleavage by acid once sufficient mass has been appended to the phenyl ring to ensure involatility. By contrast, 4-oxopiperidine electrophiles, which have been used previously to trap phenyllithium *en route* to labelled 4-phenylpiperidine derivatives, give moderate yields and liberate significant quantities of benzene.[9,10] Step b would comprise chemoselective transition metal catalysed borylation[11–15] of the phenyl ring to give an anchored phenylboronic ester group for subsequent Pd-catalysed elaboration. Following appropriate elaboration, acid-mediated *ipso*-protodegermylation[16] would constitute step d, cleaving the aryl–Ge bond and liberating the now involatile labelled derivative from the phase-tag. All purification steps prior to step d would benefit from rapid purification by fluorous solid phase extraction (SPE).[2]

In the event, bromobenzene underwent bromine–lithium exchange on treatment with *t*-BuLi at low temperature and the resulting phenyl lithium was transmetallated with an excess of fluorous-tagged germyl bromide **3**§ to give phenylgermane **4** in 97% yield (from bromobenzene) following fluorous SPE. Analysis of the crude reaction mixture by both GC and ^{1}H NMR spiking experiments revealed the mass balance to be benzene (Scheme 2).



Scheme 2 *Step a*: anchoring bromobenzene to germyl chloride **3**.

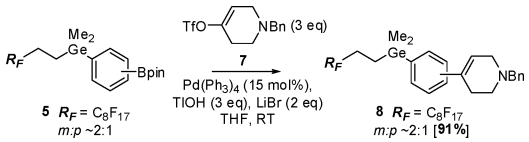
The chemoselective CH activation–borylation of phenylgermane **4** proved quite challenging. This type of process has generally been reported on simple aryl substrates catalysed by either Ir or Rh complexes with the former displaying superior selectivity for aryl *vs.* alkyl CH activation and also greater sensitivity to steric effects.[11–15] Extensive experimentation resulted in the development of optimised conditions for selective borylation of phenylgermane **4** by B_2pin_2 using $[IrCl(COD)]_2$[17]–4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as the catalyst system in octane at 125 °C (Scheme 3).



Scheme 3 *Step b*: Ir-catalysed borylation of phenylgermane **4**.

In accord with the findings of Ishiyama *et al.*,[14] dtbpy proved to be superior to 2,2′-bipyridine (bpy) as a ligand for these reactions, although in our hands $[Ir(OMe)(COD)]_2$,[18] either pre-formed or prepared *in situ*, gave essentially identical results with both these ligands to those obtained using the more easily prepared chloride complex. Use of octane as solvent resulted in significantly higher reaction rates relative to hexane, probably due to the improved solubility of the Ir–dtbpy complex;[15] the reactions did not proceed at all in THF[19] or 1,4-dioxane.[20] A reaction temperature of at least 120 °C (in a sealed vial) was required and microwave heating was unsuccessful in our hands. The formation of diborylated¶ arylgermane **6** could not be avoided even under the optimised conditions which gave a crude ratio of 14 : 70 : 16 for compounds **4** : **5** : **6** by ^{1}H NMR after 48 h. Fortunately, diborylated arylgermane **6** and the unreacted starting material **4** were readily removed by fluorous SPE from the co-eluting *meta* and *para* isomers of the desired mono-borylated arylgermane **5** ($m : p \sim 2 : 1$) which was isolated in 62% yield. As the final cleavage from the phase-tag is 'traceless' (step d, Scheme 1) both regioisomers eventually deliver the same compound.

Elaboration of boronic esters **5** into the target piperidine derivatives **1** and **2** required a Suzuki reaction with an *N*-protected piperidinyl vinyl triflate. This also proved to be a difficult reaction but was eventually efficiently accomplished using coupling conditions developed by Kishi and co-workers employing TlOH[21] as the base and LiBr as an additive. Using these conditions, *N*-benzyl protected piperidinyl vinyl triflate **7** coupled with boronic esters **5** to give styrene **8** in 91% yield (Scheme 4).

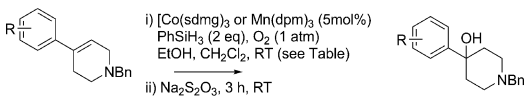


Scheme 4 *Step c (pt1)*: Pd-catalysed cross-coupling.

In order to access acetylaminopiperidine **1** we next required a method to regioselectively hydroaminate the styrenyl alkene so as to introduce the amino group at the *tert*-benzylic position. Since various direct hydroamination protocols proved unsuccessful,[22–25] we decided to effect a metal catalysed hydration reaction with a view to performing a subsequent Ritter reaction[26] to install the acetamide function concomitant with cleavage from the phase-tag. Mukaiyama[27] and then Magnus[28,29] developed $Mn(dpm)_2$ and $Mn(dpm)_3$‖ as catalysts for the hydration of α,β-unsaturated esters, ketones and nitriles with O_2–$PhSiH_3$ and more recently Carreira and co-workers[25] have used $Co(sdmg)_3$‖ for the hydration of enynes. In the event, both the Mn and Co based systems were effective on model 1,2,3,6-tetrahydropyridine substrate **9** (88% and 78% yield, respectively) but Co was preferred for the fluorous tagged arylgermane **8**, despite this complex mediating slower reactions, because Mn proved extremely difficult to decomplex from the product. The Co could be readily removed by fluorous SPE to give the desired alcohol in 61% yield (Table 1).

As expected, treatment of Ge-bound piperidine *tert*-alcohol **10** with H_2SO_4–MeCN effected a clean one-pot Ritter reaction[30]–traceless cleavage from the phase-tag to furnish acetylaminopiperidine **1** quantitatively.** Tetrahydropyridine **2** could be formed

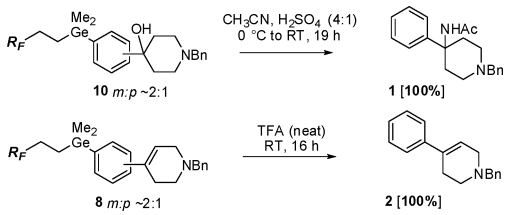
Table 1 *Step c (pt2)*: $Co(sdmg)_3$ and $Mn(dpm)_3$ catalysed hydration



Entry	Substrate	[M][a]	Duration/h	Yield (%)
1	**9**	$Mn(dpm)_3$	3[b]	88 (**11**)
2	**9**	$Co(sdmg)_3$	72	78 (**11**)
3	**8**	$Co(sdmg)_3$	24	61 (**10**)

[a] For structures see ‖. [b] Reaction carried out at 0 °C.

directly from styrene **8** by treatment with TFA, also quantitatively (Scheme 5).



Scheme 5 *Step d*: Ritter reaction–traceless cleavage (**10** → **1**) and traceless cleavage (**8** → **2**).

In summary, efficient syntheses of acetylaminopiperidine **1** (5 steps, 33% yield) and tetrahydropyridine **2** (3 steps, 55% yield) from bromobenzene have been achieved *via* a novel route in which opportunities for material losses by evaporation have been minimised in the initial immobilisation step and eliminated in subsequent steps by anchoring to a fluorous phase-tag. The key elaboration steps, all of which benefit from rapid purification by fluorous SPE, are Ir-catalysed borylation, Suzuki cross-coupling and Co-catalysed hydration. Although only a proof-of-concept study employing cold bromobenzene has been described, we anticipate that this approach could constitute a general strategy for the safe preparation of aryl-containing radiolabelled materials from [^{14}C]-bromobenzene for ADME studies. Its application and evaluation in this context is in progress.

Acknowledgements

Grateful acknowledgement is made to the EPSRC and sanofi-aventis, Alnwick for financial support.

Notes and references

‡ Preliminary, solution phase studies towards the approach described here were presented at the 9th International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006, see: A. C. Spivey, L. J. Martin, C. Noban, T. C. Jones, G. J. Ellames and A. D. Kohler, *J. Label. Compd. Radiopharm.*, 2007, **50**, 281–285 and A. C. Spivey, L. J. Martin, G. J. Ellames and A. D. Kohler, *J. Label. Compd. Radiopharm.*, 2007, **50**, 607–608.

§ Fluorous-tagged germyl bromide **3** is readily prepared in 4 steps (62% yield overall) from commercial $1H_2,2H_2$-perfluorodecyl iodide (£18/25 g: www.fluorochem.net) and germanium(II) chloride·1,4-dioxane complex (£114.50/10 g: www.sigmaaldrich.com), see Supplementary Material (ESI).

¶ Diborylation has not previously been noted in these types of reactions, probably because the borane is invariably employed as the limiting reagent (with the aryl component often deployed in great excess) or on di-substituted aryl substrates for which diborylation is precluded on steric grounds.

‖ $Co(sdmg)_3$ = Co(III)–*N*-salicyliminodimethylglycine complex (complex **1** in ref. 23); $Mn(dpm)_3$ = Mn(III)–dipivaloylmethane complex (complex **1** in ref. 24).

** The nature of the *N*-protecting group is critical for this reaction. Model *N*-Bn substrate **11** also gives the expected acetamide quantitatively on exposure to the Ritter conditions (*cf.* Scheme 5) whereas its *N*-Cbz congener suffers quantitative elimination to a styrene under identical conditions. Direct application of the Ritter conditions to styrene **9** gave the acetamide product in just 30% yield after 6 d.

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