Light-fluorous safety-catch arylgermanes – exceptionally robust, photochemically activated precursors for biaryl synthesis by Pd(0) catalysed cross-coupling†

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A new class of arylgermane derivative that participate efficiently in Pd(0)-catalysed cross-coupling reactions with aryl bromides following photochemical activation is described.

Biaryls are 'privileged' constituents of natural products, pharmaceuticals, agrochemicals, dyes, organic semiconductors, liquid crystals and ligands/auxiliaries for asymmetric synthesis.[1] They are generally prepared by transition metal catalysed cross-coupling reactions between *e.g.* aryl–magnesium, –zinc, –tin, –silicon or –boron compounds and aryl halides.[2] All these aryl metals are, however, also reactive towards major classes of reagents commonly used in organic synthesis (*e.g.* bases and nucleophiles). Consequently, they are rarely carried through synthetic sequences prior to their deployment for cross-coupling. This limitation applies particularly when contemplating the use of an aryl metal bond as the key component of a linker for phase-tagged parallel synthesis which could undergo cleavage from the phase tag concomitant with cross-coupling to afford biaryl-containing libraries.[3]

The reactivity of an aryl metal species, to a first approximation, inversely correlates with the electronegativity of the metal (*i.e.* Mg > Zn > Sn > Si > B). Hence, aryltrifluoroborate salts (which show notable stability towards oxidants)[4] and aryl triallylsilanes[5] have emerged as the most robust biaryl cross-coupling precursors to date. Other 'safety-catch' silyl groups[6] such as the benzyldimethylsilyl (BDS) group,[7] which can withstand some conditions for silyl ether deprotection but which can be activated to give silanol reactive intermediates by treatment with TBAF, have also proved useful for cross-coupling of alkenyl systems. The salt properties of the trifluoroborates and the inherent polarity of C–Si bonds, however, limit the stability of all these groups, in particular towards bases and nucleophiles.[8]

We envisaged that more robust safety-catch cross-coupling partners for biaryl synthesis could be developed by employing arylgermane derivatives. Although Ge is located between Si and Sn in the periodic table, the electronegativity of Ge is the closest to that of C among group 14 elements (C, 2.50; Si, 1.74; Ge, 2.02; Sn, 1.72).[9] This scandide contraction effect[10] renders C–Ge bonds less polar than C–Si and C–Sn bonds. Consequently, arylgermanes possess significantly greater stability than their Si and Sn congeners towards bases and nucleophiles,[11] exhibit lower toxicity,[12] and require activation of the C–Ge bond for Pd(0)-catalysed cross-coupling.[13] They display slightly higher reactivity towards acids and electrophiles than their Si congeners.[14]

Here, we describe the scope of a new biaryl cross-coupling method that employs light fluorous[15] aryl bis(2-naphthylmethyl)-germanes as robust safety-catch coupling precursors. These derivatives display exceptional levels of stability towards bases and nucleophiles and allow for purification using fluorous SPE[15] prior to cross-coupling making them particularly attractive for parallel synthesis of high value biaryls.

In previous studies we have shown that two heteroatom substituents (*e.g.* Cl or F) on Ge are required to allow efficient Pd(0) catalysed cross-coupling between arylgermanes and aryl bromides and that 2-naphthylmethyl groups on Ge can be cleaved by photooxidation with $Cu(BF_4)_2$[16] to generate germyl fluorides.[17] Here we describe the union of these findings into a powerful method for biaryl synthesis that allows introduction of a robust, perfluorooctyl-tagged trialkylarylgermane early in a synthesis for subsequent photolytic activation then cross-coupling with cleavage from the phase-tag. The scope of the method has been explored for a range of arylgermanes and aryl bromides (Table 1).

Arylgermanes **1a–f** are readily prepared by reaction of the aryl lithium or Grignard reagents with bis(2-naphthylmethyl)germyl bromide, which in turn is easily prepared from commercially available $1H_2,2H_2$-perfluorooctyl iodide and germanium(II) chloride dioxane complex in four steps ($\sim$50% yield overall, see ESI†). The photolytic activation process entails irradiation of a solution of the arylgermane in a Pyrex Schlenk tube using a high pressure Hg lamp (125 W) for $\sim$2 h. The progress of the photooxidation reaction is not appreciably dependent on the nature of the aryl group and can be monitored conveniently by ^{19}F NMR.‡ Following evaporation of the solvent, dissolution of the residue in CH_2Cl_2 and washing with water to remove Cu salts, the crude difluorogermane is subject directly to the TBAF-promoted cross-coupling. The 2-naphthylmethyl ether photooxidation by-product can be removed by sublimation at the difluorogermane stage but does not interfere with the cross-coupling reaction.

Electron poor and electron rich arylgermanes and aryl bromides can be coupled using this method and optimal yields are achieved

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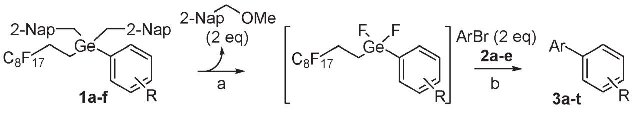
Table 1 Photoactivation/cross-coupling of arylgermanes **1a–f**



Reagents and conditions: (a) *hν*, Pyrex tube, $Cu(BF_4)_2 \cdot nH_2O$ (2 × 3 equiv.), MeOH–MeCN (3 : 1), 2 h; (b) $PdCl_2(MeCN)_2$ (10 mol%), $P(2\text{-}Tol)_3$ (15 mol%), $TBAF \cdot 3H_2O$ (2.7 equiv.), CuI (1 equiv.), DMF, 120 °C, 16 h.

Entry	R	Ar	Yield (%)
1	4-OMe (**1a**)	3,5-$(CF_3)_2C_6H_3$ (**2a**)	96 (**3a**)
2	4-OMe (**1a**)	4-ClC_6H_4 (**2b**)	85 (**3b**)
3	4-OMe (**1a**)	4-$BnOC_6H_4$ (**2c**)	65 (**3c**)
4	4-OMe (**1a**)	1-Naphthyl (**2d**)	75 (**3d**)[a]
5	4-Me (**1b**)	3,5-$(CF_3)_2C_6H_3$ (**2a**)	84 (**3e**)
6	4-Me (**1b**)	4-ClC_6H_4 (**2b**)	69 (**3f**)
7	4-Me (**1b**)	4-$BnOC_6H_4$ (**2c**)	48 (**3g**)
8	4-Me (**1b**)	1-Naphthyl (**2d**)	71 (**3h**)
9	H (**1c**)	3,5-$(CF_3)_2C_6H_3$ (**2a**)	74 (**3i**)
10	H (**1c**)	4-ClC_6H_4 (**2b**)	63 (**3j**)
11	H (**1c**)	4-$BnOC_6H_4$ (**2c**)	40 (**3k**)
12	H (**1c**)	1-Naphthyl (**2d**)	60 (**3l**)
13	4-Cl (**1d**)	3,5-$(CF_3)_2C_6H_3$ (**2a**)	71 (**3m**)
14	4-Cl (**1d**)	4-$BnOC_6H_4$ (**2c**)	42 (**3n**)
15	4-Cl (**1d**)	1-Naphthyl (**2d**)	75 (**3o**)
16	4-Cl (**1d**)	2-$NO_2C_6H_4$ (**2e**)	61 (**3p**)
17	2-OMe (**1e**)	3,5-$(CF_3)_2C_6H_3$ (**2a**)	65 (**3q**)
18	2-OMe (**1e**)	4-ClC_6H_4 (**2b**)	49 (**3r**)
19	2-OMe (**1e**)	4-$BnOC_6H_4$ (**2c**)	11 (**3s**)[b]
20	2-OMe (**1e**)	1-Naphthyl (**2d**)	27 (**3t**)
21	4-CF_3 (**1f**)	3,5-$(CF_3)_2C_6H_3$ (**2a**)	26 (**3u**)[b]
22	4-CF_3 (**1f**)	4-ClC_6H_4 (**2b**)	11 (**3v**)[b]

[a] *cf.* 1-NapI/LiBr (12%[b]), 1-NapCl/LiBr (<1%[b]), 1-NapOTf/LiBr (0%[b]). [b] GC yield.

with electron rich arylgermanes and electron poor aryl bromides (*e.g.* entries 1 and 5). 4-Trifluoromethylphenylgermane **1f** appears to represent the limit with respect to electron deficiency that can be tolerated in the arylgermane partner (entries 21 and 22). Steric hindrance also reduces yields (*e.g. cf.* entry 4 *vs.* 20). Aryl iodides couple poorly and aryl-chlorides and -triflates do not couple under these conditions (entry 4, note a).

The stability of the fluorous-tagged bis(2-naphthylmethyl) arylgermanes was assessed by subjecting phenylgermane **1c** to a series of stressing conditions and monitoring its recovery by HPLC against an internal standard (Table 2).

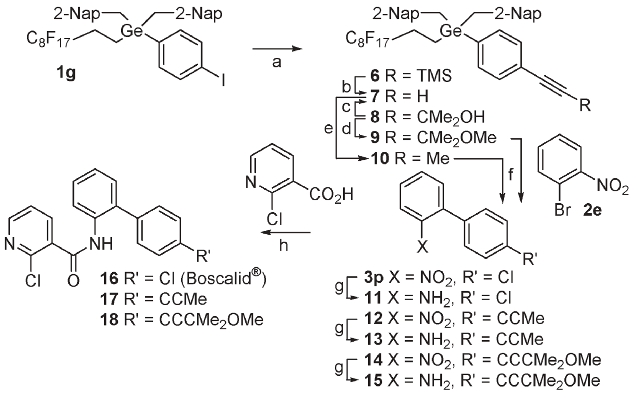
As expected, germane **1c** proved to be stable to all but the oxidative and acidic conditions (entries 7 and 8). Its stability to fluoridolytic conditions used widely for the deprotection of silyl ethers is particularly notable (entry 6).

Table 2 Stability profile of fluorous-tagged phenylgermane **1c**

Entry	Conditions[a]	% Recovery of **1c**[b]
1	$NaBH_4$, THF	107
2	$LiAlH_4$, THF	104
3	Hydrazine–DMF (2% v/v)	104
4	$HS(CH_2)_2OH$, DBU, DMF	102
5	Piperidine–DMF (20% v/v)	101
6	TBAF, THF	102
7	*m*-CPBA, CH_2Cl_2	76
8	TFA–CH_2Cl_2 (50% v/v)	20

[a] All reagents (5 equiv.) for 3 h at RT; [b] By HPLC *vs.* internal standard [9-methylanthracene (**4**) or 4,4′-di-*tert*-butylbiphenyl (**5**)]; average of two runs (±10%) (see ESI).

To underscore the stability of these new germanium derivatives to conditions hitherto incompatible with any other cross-coupling precursors, we have deployed them in the synthesis of alkynyl derivatives **17** and **18**[18] of the commercially important agrochemical fungicide Boscalid® (**16**) (Scheme 1).



Scheme 1 Synthesis of Boscalid® (**16**) and derivatives **17** and **18**. *Reagents and conditions*: (a) HCCTMS or $HCCCMe_2OH$, $Pd(OAc)_2$, PPh_3, CuI, $^{n}BuNH_2$ [**6** (52%); **8** (68%)]; (b) K_2CO_3, KF (67%); (c) KOH, 120 °C (98%); (d) $^{n}BuLi$, MeOTf (87%); (e) NaH, Me_2SO_4, (87%); (f) as Table 1 [**9** → **14** (50%); **10** → **12** (54%)]; (g) $SnCl_2$ [**11** (88%); **13** (80%); **15** (80%)]; (h) DCC, DMAP [**11** → **16** (65%); **13** → **17** (59%); **15** → **18** (68%)].

Boscalid® itself was prepared from nitrobiaryl **3p** (Table 1, entry 16) by $SnCl_2$ reduction then DCC mediated amidation with 2-chloronicotinic acid. Synthesis of its alkynyl analogues **17** and **18** from nitrobiaryls **13** and **15** started from arylgermane **1g** and required the germane group to survive Sonogashira coupling conditions (**1g** → **6**; **1g** → **8**), alkynyl-TMS fluoridolysis (**6** → **7**), KOH-mediated alkynyldimethylcarbinol fragmentation (**8** → **7**) and NaH/Me_2SO_4 and $^{n}BuLi$/MeOTf alkylation conditions (**8** → **9**; **7** → **10**) prior to the photolytic activation/cross-coupling steps (**9** → **14**; **10** → **12**). It is very doubtful that any other arylmetal cross-coupling precursor could have survived these sequences of reactions.

In summary, light-fluorous bis(2-naphthylmethyl)arylgermanes constitute very robust precursors for Pd(0)-catalysed synthesis of biaryls. They are exceptionally stable towards bases and nucleophiles. This feature allows for their introduction early in multi-step synthetic sequences involving these reagent classes. This and the favorable purification attributes imparted by the phase tag should make them attractive in particular for the parallel synthesis of biaryl libraries for property screening.

We are currently developing the method for parallel synthesis using automated fluorous SPE with UV diode/fiber-optic light delivery.

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Notes and references

‡ The mono-fluoro intermediate forms in ∼10 min (singlet at δ_F *ca.* −203 ppm); this converts more slowly into three signals at between δ_F *ca.*

−163 and −165 ppm. Studies are ongoing to fully characterise this apparent mixture of the difluorogermane and derivative(s).

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