

Arylchlorogermanes/TBAF/“Moist” Toluene: A Promising Combination for Pd-Catalyzed Germyl-Stille Cross-Coupling

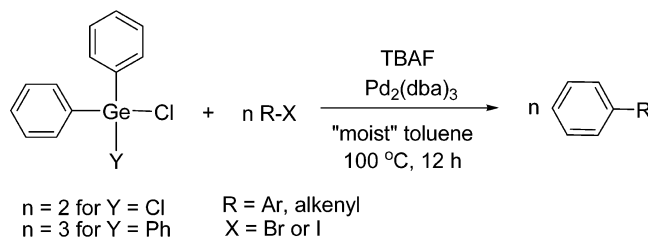
Zun-Ting Zhang,[†] Jean-Philippe Pitteloud, Laura Cabrera, Yong Liang, Myrdich Toribio, and Stanislaw F. Wnuk*

Department of Chemistry and Biochemistry, Florida International University, Miami, Florida 33199

wnuk@fiu.edu

Received December 15, 2009

ABSTRACT



The trichlorophenyl-, dichlorodiphenyl-, and chlorotriphenylgermanes undergo Pd-catalyzed cross-couplings with aryl bromides and iodides in the presence of TBAF in toluene with addition of the *measured* amount of water. One chloride ligand on the Ge center allows efficient activation by fluoride to promote transfer of one, two, or three phenyl groups from the organogermane precursors.

The Pd-catalyzed cross-coupling of organogermanes has thus far received much less attention¹ than the couplings involving organostannanes and organosilanes.² This is due to the lower reactivity of tetracoordinated organogermanium species, the less developed syntheses of vinyl/aryl germanyl derivatives, and the higher cost of germanium relative to silicon.³ The carbagermatranes **1**, with internal coordination of nitrogen to germanium, were the first examples of reactive tetracoordinated germanes applied to Pd-catalyzed cross-coupling reactions with aryl bromides⁴ (Figure 1). The oxagermatranes

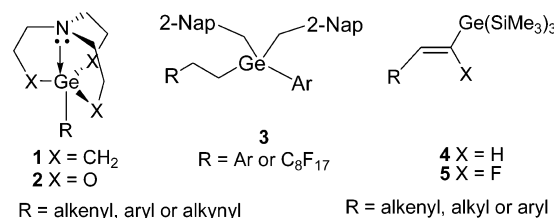


Figure 1. Organogermanes utilized in Pd-catalyzed couplings.

[†] On faculty leave from School of Chemistry and Materials Science, Shaanxi Normal University, Xi'an, P.R. China.

(1) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *1*, 211–226.

(2) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(3) *The Chemistry of Organic Germanium, Tin and Lead Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1995; Vol. 1 and 2002; Vol. 2.

(4) Kosugi, M.; Tanji, T.; Tanaka, Y.; Yoshida, A.; Fugami, K.; Kameyama, M.; Migita, T. *J. Organomet. Chem.* **1996**, *508*, 255–257.

2 were found to be more efficient than carbagermatranes and triethoxygermanes.^{5,6} Fluoride-promoted couplings with aryltri(2-furyl)germanes⁷ and NaOH-activated couplings with

(5) Faller, J. W.; Kultyshev, R. G. *Organometallics* **2002**, *21*, 5911–5918.

(6) Faller, J. W.; Kultyshev, R. G.; Parr, J. *Tetrahedron Lett.* **2003**, *44*, 451–453.

arylgermanium trichlorides⁸ or their hydrolyzed and stable sesquioxide alternatives⁹ were also reported. The bis-(2-naphthylmethyl)arylgermanes **3** were developed as photochemically activated arylgermanes for the synthesis of biaryls.^{10,11} The vinyl tris(trimethylsilyl)germanes **4** were employed as transmetalation reagents in “ligand- and fluoride-free” coupling reactions with halides under oxidative conditions (H₂O₂).^{12,13} The (α-fluoro)vinyl germanes **5** gave access to fluoroalkenes¹⁴ although application of (α-fluoro)vinyl stannanes and silanes to couplings has had limited success.^{15,16} Recently, couplings of vinyltributylgermanes with aryl halides were found to occur more efficiently under Heck than Stille conditions to give preferentially Z-alkenes.¹⁷

In general, couplings with organogermanes appear to be promoted by: (i) activation of germanium by internal coordination/chelation,^{4,5,17} (ii) formation of the hypervalent species with germanium–oxygen bonds;^{7–9,13} and (iii) the presence of two labile heteroatom ligands (e.g., Cl or F) on Ge atom.^{10,11} Herein, we report that chlorophenylgermanes with at least one labile chloride ligand are activated by fluoride in “moist” toluene to allow efficient transfer of up to three phenyl groups from germane precursors during Pd-catalyzed coupling reactions with aryl halides.

Treatment of PhGeMe₂Cl **6** with 1-iodonaphthalene in the presence of tetrabutylammonium fluoride (TBAF) and tris-(dibenzylideneacetone)dipalladium(0) [Pd₂(dba)₃] in toluene gave cross-coupling product **7a** in addition to the binaphthyl homocoupling byproduct **8a** (Table 1). The amount of TBAF was found to be crucial for the successful coupling (entries 1–5). At least 4 equiv of TBAF were required to produce **7a** in maximum yield. Other Pd catalysts afforded **7a** in lower yields and a decreased ratio of **7a** to **8a** (entries 6–7). Replacing 1 M TBAF/THF solution with neat TBAF·3H₂O also gave product **7a** (entry 8). Coupling in the presence of Me₄NF, CsF, or NH₄F instead of TBAF failed to produce **7a**. The reaction also proceeded successfully at 80 °C (80%; 10:1) and 110 °C (93%; 10:1) as well as at reflux in benzene (90%; 10:1), requiring 12 h for the best results (entry 4).

Toluene was the obvious solvent choice since attempts in DMSO (5%, 110 °C) or THF at reflux (0%) or dioxane at reflux (59%; 3:1) failed or afforded **7a** in lower yields. Higher yield for the coupling in dioxane than in THF may be

Table 1. Effect of Various Reaction Parameters on the Efficiency of Cross-Coupling of Chlorodimethylgermane **6** with 1-Iodonaphthalene^a

entry	Pd	TBAF ^b	7a [yield(%)] ^c	ratio (7a : 8a)
1	Pd ₂ (dba) ₃	1.0	19	1:1
2	Pd ₂ (dba) ₃	2.0	61	9:1
3	Pd ₂ (dba) ₃	3.0	79	17:1
4	Pd ₂ (dba) ₃	4.0	93 ^{d,e}	20:1
5	Pd ₂ (dba) ₃	5.0	94	12:1
6	Pd(OAc) ₂	4.0	58	5:2
7	Pd(PPh ₃) ₄	4.0	5	2:1
8	Pd ₂ (dba) ₃	4.0 ^f	70	6:1

^a Couplings were performed on 0.14 mmol scale of **6** (0.04 M) with 1.1 equiv of 1-iodonaphthalene and 0.09 equiv of Pd catalyst. ^b Commercial 1 M THF solution containing 5% of water, unless otherwise noted. ^c Determined by GC-MS of the crude reaction mixture. ^d Isolated yield. ^e After 4 h, 49% (8:1); 8 h, 78% (15:1). ^f With TBAF·3H₂O.

attributable to the increased temperature of the reaction as well the difference in dielectric constant [7.58 for THF as compared to dioxane (2.21) and toluene (2.15)].¹⁸ Bases such as NaOH [Pd(OAc)₂; dioxane/H₂O, 2:1] or KOSiMe₃ [Pd₂(dba)₃, toluene], instead of TBAF, failed or were less efficient in promoting couplings.

We next examined couplings of Ph₂GeCl₂ **9** or Ph₃GeCl **10** with 1-iodonaphthalene. Treatment of **9** with 1.1 equiv of iodide and 7 equiv of TBAF gave **7a** (Table 2, entry 1). Coupling of **9** with 2.2 equiv of 1-iodonaphthalene also resulted in total consumption of iodide to afford **7a** and **8a** (entry 2). Interestingly, couplings in toluene with addition of the *measured* amount of water (1 M TBAF/THF/H₂O; ~1:5 M/M) gave a higher yield of **7a** with a superior ratio of **7a**:**8a** (entries 3 vs 1 and 4 vs 2). An investigation of the coupling reactions with different amounts of water, revealed that addition of 100 μL of H₂O (~40 equiv) gave optimal yields (entry 10). Two phenyl groups were efficiently transferred in the presence of excess iodide (e.g., 89%, entry 4; yield is based upon two phenyl groups transferring from the chlorogermane reagent **9**). Halides are often used in couplings as limiting reagents to reduce formation of homocoupling byproducts and the yields are based on the halide components unlike herein.

Couplings of **10** with 1.1, 2.2, or 3.3 equiv of 1-iodonaphthalene proceeded with efficient transfer of up to three phenyl groups to give **7a** (entries 5–10). [See Supporting Information for the GC/MS of the crude reaction mixture between **9** or **10** with 1-iodonaphthalene (entries 4 and 10).] Again, yields and **7a**:**8a** ratios increased when wet toluene was used. Atom-efficient Stille cross-couplings of Ar₄Sn with aryl halides, where all four substituents on tin participate in the

(7) Nakamura, T.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3165–3167.

(8) Enokido, T.; Fugami, K.; Endo, M.; Kameyama, M.; Kosugi, M. *Adv. Synth. Catal.* **2004**, *346*, 1685–1688.

(9) Endo, M.; Fugami, K.; Enokido, T.; Sano, H.; Kosugi, M. *Adv. Synth. Catal.* **2007**, *349*, 1025–1027.

(10) Spivey, A. C.; Tseng, C.-C.; Hannah, J. P.; Gripton, C. J. G.; de Fraine, P.; Parr, N. J.; Scicinski, J. J. *Chem. Comm.* **2007**, 2926–2928.

(11) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P.; Tseng, C.-C.; Fraine, P. D.; Parr, N. J.; Scicinski, J. J. *Appl. Organometal. Chem.* **2007**, *21*, 572–589.

(12) Wnuk, S. F.; Garcia, P. I., Jr.; Wang, Z. *Org. Lett.* **2004**, *6*, 2047–2049.

(13) Wang, Z.; Wnuk, S. F. *J. Org. Chem.* **2005**, *70*, 3281–3284.

(14) Wang, Z.; Gonzalez, A.; Wnuk, S. F. *Tetrahedron Lett.* **2005**, *46*, 5313–5316.

(15) Chen, C.; Wilcoxon, K.; Zhu, Y. F.; Kim, K. i.; McCarthy, J. R. *J. Org. Chem.* **1999**, *64*, 3476–3482.

(16) Hanamoto, T.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 6354–6359.

(17) Torres, N. M.; Lavis, J. M.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **2009**, *50*, 4407–4410.

(18) Segansh, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 1137–1143.

Table 2. Cross-Coupling of Chlorophenylgermanes **9** and **10** with 1-Iodonaphthalene Promoted by TBAF and TBAF/H₂O

entry	germane	RX (equiv)	method ^a	7a [yield(%)] ^b	ratio (7a:8a)
1	9	1.1	A	32 ^c (30)	2.7:1
2	9	2.2	A	58 (55)	2.2:1
3	9	1.1	B	45 (42)	23:1
4	9	2.2	B	91 (89)	10:1
5	10	1.1	A	13 ^d (12)	1:1.4
6	10	2.2	A	37 (35)	2:1
7	10	3.3	A	40 (39)	1.2:1
8	10	1.1	B	18 (17)	2.5:1
9	10	2.2	B	60 (60)	9:1
10	10	3.3	B	95 ^e (88)	13:1

^a Method A: Couplings were performed on 0.14 mmol scale of germane (0.04 M) with Pd₂(dba)₃ (0.09 equiv) and 7 equiv of TBAF (1M/THF). Method B: as in Method A with addition of H₂O (100 μL). ^b Based upon transferring two phenyl groups from **9** or three phenyl groups from **10**. Determined by GC-MS of the crude reaction mixture (isolated yields in parentheses). ^c 26% and 31% with 6 and 8 equiv of TBAF. ^d 11% and 14% with 6 and 8 equiv of TBAF. ^e 57% (3.8:1) with 50 μL H₂O; 82% (7:1) with 150 μL H₂O.

carbon–carbon bond formation, are known.^{19,20} Also, vinylpolysiloxanes were showed to transfer each of their vinyl groups during Pd-catalyzed couplings with aryl and alkenyl iodides in the presence of TBAF.²¹ However, attempts to induce multiple transfer of the phenyl group during fluoride-promoted couplings of (allyl)_xPh_{4-x}Si (*x* = 1 or 2) with aryl halides failed.²²

Couplings of **9** or **10** with other aryl, alkenyl, and heterocyclic iodides and bromides (using 2.2 or 3.3 equiv of halides, respectively) promoted by TBAF/H₂O are presented in Table 3 (entries 1–14). Reactions of germanes **9** or **10** with reactive 4-iodoacetophenone produced **7d** in low yields in addition to large quantities of the reductive homocoupling byproduct **8d**. However, coupling of the less reactive 4-bromoacetophenone at higher temperature (115 °C) resulted in better yields and improved **7d:8d** ratios (entries 5 vs 4 and 12 vs 11). Treatment of PhGeCl₃ **11** with halides and TBAF/toluene or wet toluene also afforded coupling products **7** (entries 15–22), although it has been reported that fluoride ion did not promote the couplings of PhGeCl₃ with aryl halides.⁸ It appears that reactivity of the chlorogermanes increases with the number of halogen ligands on the Ge center (**10** < **9** < **11**). As expected,⁷ coupling attempts with Ph₄Ge failed reinforcing the needs for at least one labile heteroatom ligand at the Ge center. The necessity

Table 3. Cross-Coupling of Chlorogermanes **9–11** with Halides^a

entry	germane	halide	product	yield (%) ^b	ratio (7:8)
1	9	1-Bromonaphthalene ^c	7a	54 (48)	7.2:1
2	9	(4)CH ₃ OPI	7b	86 ^d (85)	9.8:1
3	9	(3)CF ₃ PI	7c	70 (68)	3.4:1
4	9	(4)CH ₃ COPhI	7d	12 (10)	3:2
5	9	(4)CH ₃ COPhBr	7d	26 ^d (21)	99:1
6	9	PhCH=CHBr	7e	8 ^{e,f} (5)	1:3
7	9	2-Iodo-5-Me-thiophene	7f	13 ^e (6)	2:3
8	10	1-Bromonaphthalene	7a	24	1.4:1
9	10	(4)CH ₃ OPI	7b	48 ^f (40)	4:1
10	10	(3)CF ₃ PI	7c	48	3:2
11	10	(4)CH ₃ COPhI	7d	3	1:20
12	10	(4)CH ₃ COPhBr	7d	24 ^d	1:1
13	10	PhCH=CHBr	7e	3 ^g	1:8
14	10	2-Iodo-5-Me-thiophene	7f	3 ^g	2:3
15	11	1-Iodonaphthalene	7a	99 ^h (96)	35:1
16	11	1-Bromonaphthalene	7a	90 ^g (82)	99:1
17	11	(4)CH ₃ OPI	7b	88 ^g (80)	10:1
18	11	(3)CF ₃ PI	7c	93 (87)	9:1
19	11	(4)CH ₃ COPhI	7d	99 (88)	99:1
20	11	(4)CH ₃ COPhBr	7d	91	99:1
21	11	PhCH=CHBr	7e	30 ^{h,g} (28)	3:1
22	11	2-Iodo-5-Me-thiophene	7f	48 ^{h,g} (35)	3:2

^a Couplings were performed on 0.14 mmol scale of germanes (0.04 M) with 0.09 equiv of Pd catalyst, 1.1 (**11**), 2.2 (**9**) or 3.3 (**10**) equiv of halides and TBAF/(1 M/THF, 7 equiv)/water (100 μL). ^b Based upon transferring of one, two or three phenyl groups from **11**, **9** or **10**, respectively. Determined by GC-MS of the crude reaction mixture (isolated yields in parentheses). ^c Coupling with 1-chloronaphthalene failed. ^d 115 °C. ^e Biphenyl was also produced (~25–50%). ^f 28 h. ^g Without H₂O. ^h 88% (81%, 19:1) without H₂O.

of two halogen ligands had been proposed for nucleophilic activation by F[−] or OH[−] ions.¹¹

TBAF most likely facilitates the coupling by generating the more reactive hypervalent fluorogermanium species. It is viable that the germanium species with extra halogen ligands formed after each transmetalation cycle is rendered more reactive to efficiently transfer a second or third phenyl group from the Ge atom. Reactivity of these hypervalent Ge species could be superior in toluene solvent due to the weak solvation. Water might play multiple roles in enhancing the efficiency of the couplings as was found with organosilanes, including the formation of the reactive hydroxypalladium intermediates.^{1,23,24} For example, the hydration level of Cs₂CO₃ and CsOH were found to be a decisive factor during the coupling of the aryl(dimethyl)silanol with aryl halides.²⁵ Also, Denmark and Sweis showed that water was a critical additive in the fluoride promoted reaction of alkenylsilanol

(19) Fugami, K.; Fugami, K.; Ohnuma, S.-y.; Kameyama, M.; Saotome, T.; Kosugi, M. *Synlett* **1999**, 1999, 63–64.

(20) Zhou, W.-J.; Wang, K.-H.; Wang, J.-X. *J. Org. Chem.* **2009**, *74*, 5599–5602.

(21) Denmark, S. E.; Wang, Z. *J. Organomet. Chem.* **2001**, *624*, 372–375.

(22) Sahoo, A. K.; Oda, T.; Nakao, Y.; Hiyama, T. *Adv. Synth. Catal.* **2004**, *346*, 1715–1727.

(23) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865–4875.

(24) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876–4882.

(25) Denmark, S. E.; Ober, M. H. *Adv. Synth. Catal.* **2004**, *346*, 1703–1714.

with phenyl nonaflate.^{1,26} In addition, the fluorination of the bulky chlorogermanes may be accelerated by the addition of water as was reported for hindered chlorosilanes.²⁷

Mixing of **6** with TBAF in benzene-*d*₆ at ambient temperature showed the formation of a distinctive septet at $\delta -194.3$ ($^3J_{\text{F-H}} \sim 6.0$ Hz) for PhGeMe₂F in agreement with the literature report for similar compounds.¹¹ Prolonged time and/or heating promoted equilibration with perfluorinated species [$\delta -150.8$ (br s), -126.4 (br s)] analogous to the reported hypervalent tin^{28–30} and silicon^{31–33} species, which were successfully utilized in cross-coupling reactions.

We have demonstrated that arylchlorogermanes undergo Pd-catalyzed cross-couplings with aryl halides in the presence

of TBAF in wet toluene. One chloride ligand on Ge center allows efficient activation by fluoride to promote transfer of up to three aryl groups from germane. The methodology shows that organogermanes can render a coupling efficiency comparable to the more established stannane and silane counterparts.

Acknowledgment. We thank NIGMS/NCI(1SC1CA138176) and the Overseas Scholarship Program of Shaanxi Normal University (Z.T.Z.), FIU's Dissertation Year Fellowship (J.P.P.) and MARC U*STAR (GM083688-02) (L.C.) for their support.

Supporting Information Available: General experimental details and GC/MS and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL9028918

-
- (26) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771–3774.
(27) Lickiss, P. D.; Lucas, R. J. *Organomet. Chem.* **1996**, *510*, 167–172.
(28) Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381–7384.
(29) Garcia Martinez, A.; Osio Barcina, J.; Colorado Heras, M. d. R.; de Fresno Cerezo, A. *Organometallics* **2001**, *20*, 1020–1023.
(30) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119–122.
(31) Pilcher, A. S.; Ammon, H. L.; DeShong, P. J. *Am. Chem. Soc.* **1995**, *117*, 5166–5167.
(32) Mowery, M. E.; DeShong, P. J. *Org. Chem.* **1999**, *64*, 3266–3270.

-
- (33) Handy, C. J.; Lam, Y.-F.; DeShong, P. J. *Org. Chem.* **2000**, *65*, 3542–3543.