Palladium-Catalyzed Cross-Coupling Reaction by Means of Organogermanium Trichlorides

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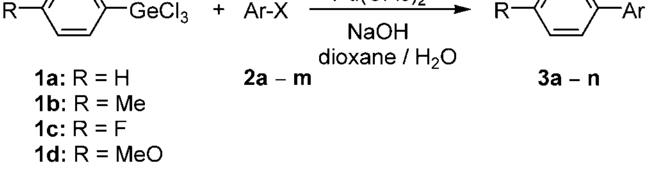
Abstract: Easily accessible arylgermanium trichlorides were found to undergo palladium-catalyzed cross-coupling reactions with aryl bromides and iodides in good yields. The reaction is performed in an aqueous medium with sodium hydroxide as an activator. Some base-sensitive functionalities such as acetyl and trifluoromethyl survived the reaction.

Keywords: aqueous reaction medium; aryl halides, cross-coupling; germanium; hypervalent compounds; palladium

The organotin–mediated cross-coupling reaction is one of the most powerful protocols for constructing carbon skeletons because of its compatibility with a wide variety of reactive functionalities.[1] Due to its hazardous by-product, increasing attention has recently been paid to less hazardous alternative reagents such as boron[2] and silicon[3] counterparts. Organogermanium coupling has been much less investigated while it can also be a promising substitute.[4] Apart for its cost, the problem is the limited availability of reactive organogermanium reagents. We have recently developed a fluoride ion-mediated, highly efficient organotin-cross-coupling reaction.[5] It further turned that the reaction could also be promoted by alkali hydroxide.[6] We report here our results on the palladium-catalyzed cross-coupling reaction using readily available organogermanium trichlorides[7] in aqueous alkaline solution.[8]



(1)

The arylgermanium mixed trihalide is readily prepared by the reaction of an aryl halide with the dioxane complex of germanium(II) chloride.[9] Its hydrolysis followed by treatment with concentrated hydrochloric acid affords the corresponding arylgermanium trichloride in moderate to good yields.[9] Although the initially obtained mixed trihalide also acts as an efficient reagent, we used phenylgermanium trichloride as the reagent for refinement of the reaction in view of clarity. The effects of catalyst, solvent, and the amount of base were explored using 4-iodoanisole as the electrophile and the results are indicated in Table 1. On account of the substrate-to-reagent ratio, the yields of runs 1–9 are based on the germanium reagent and those of runs 10–16 on the iodide. All the experiments were carried out in mixed solvents of that indicated in Table 1 and water (4 cm^3 each for 0.5 mmol of the substrate). Potassium or sodium hydroxide was necessary to promote the reaction. The reaction in the absence of the base resulted in quantitative recovery of iodoanisole (run 1). Milder bases such as potassium and sodium carbonate did not provide the desired product at all (run 12).[11] Fluoride ion, which was expected to be effective according to the results for organotin cases,[5,12] did not promote the reaction either.[4c] The yield was maximum with 8 mol equivs. of KOH to the germanium reagent and it decreased in the presence of more or less base (runs 2–5). Palladium(II) acetate without added ligand gave the best result among all conditions examined (runs 4, 6–9). Addition of triphenylphosphine did not alter the results (runs 4 *vs.* 6, 10 *vs.* 11). As an organic co-solvent, dioxane was the most suitable (runs 13–16). The yield was even higher when sodium hydroxide was used in place of KOH (run 13).

Being encouraged by the above results, we examined the reaction between a variety of arylgermanium trichlorides and aryl halides and the results are summarized in Table 2. Moderate to excellent yields of the expected coupling products were obtained within a short time. Not only aryl iodides but also bromides reacted smoothly. It is worth noting that base-sensitive function-

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Table 1. Pd-catalyzed reaction of iodoanisole with phenyltrichlorogermane (**1a**).[a]

Run	Base (equiv)[b]		Solvent	Catalyst	Time	Yield [%][c]
1[d]	KOH	0	Dioxane	$Pd_2(dba)_3 \cdot CHCl_3/2\ PPh_3$	4	0
2[d]	KOH	4	Dioxane	$Pd_2(dba)_3 \cdot CHCl_3/2\ PPh_3$	4	trace
3[d]	KOH	6	Dioxane	$Pd_2(dba)_3 \cdot CHCl_3/2\ PPh_3$	4	34
4[d]	KOH	8	Dioxane	$Pd_2(dba)_3 \cdot CHCl_3/2\ PPh_3$	4	57
5[d]	KOH	16	Dioxane	$Pd_2(dba)_3 \cdot CHCl_3/2\ PPh_3$	4	48
6[d]	KOH	8	Dioxane	$Pd_2(dba)_3 \cdot CHCl_3$	24	61
7[d]	KOH	8	Dioxane	$Pd(OAc)_2$	4	62 (51)
8[d]	KOH	8	Dioxane	$PdCl_2$	4	40
9[d]	KOH	8	Dioxane	$PdCl_2[P(o\text{-tolyl})_3]_2$	4	46
10	KOH	8	Dioxane	$Pd(OAc)_2$	1.5	70 (64)
11	KOH	8	Dioxane	$Pd(OAc)_2/_2\ PPh_3$	1.5	70 (64)
12	Na_2CO_3	8	Dioxane	$Pd(OAc)_2$	1.5	0
13	NaOH	8	Dioxane	$Pd(OAc)_2$	1.5	82 (70)
14	NaOH	8	Toluene	$Pd(OAc)_2$	1.5	8
15	NaOH	8	DMPU	$Pd(OAc)_2$	1.5	68
16	NaOH	8	DMSO	$Pd(OAc)_2$	1.5	39

[a] All experiments were carried out using phenyltrichlorogermane (0.6 mmol) and 4-iodoanisol (0.5 mmol) in the presence of palladium catalyst (5 mol %) in the organic solvent indicated (4 mL) and water (4 mL) at 110 °C (oil-bath temperature).

[b] Molar equivalents to the germanium reagent.

[c] GC yield. Isolated yield is in parentheses.

[d] ArI/Ge = 0.6/0.5 mmol.

Table 2. Palladium-catalyzed cross-coupling reaction of Ar'-X with Ar-$GeCl_3$.[a]

Run	ArGe	Ar-X	Time [h]	Product	Yield[b] [%]
1	**1a**	4-Iodoanisole (**2a**)	1.5	**3a**[c]	70
2	**1d**	4-Bromo-*N*,*N*-dimethylaniline (**2b**)	0.5	**3b**	66
3	**1c**	4-Bromoanisole (**2c**)	1.5	**3c**[d]	48
4	**1d**	Bromobenzene (**2d**)	1	**3a**	72
5	**1d**	4-Bromoacetophenone (**2e**)	0.5	**3d**[e]	71
6	**1d**	4-Bromofluorobenzene (**2f**)	0.5	**3e**	86
7	**1c**	4-Bromonitrobenzene (**2g**)	1.5	**3f**	59
8	**1d**	**2g**	1.5	**3g**[f]	72
9	**1d**	3-Bromotrifluoromethylbenzene (**2h**)	0.5	**3h**[g]	87
10	**1c**	3-Bromonitrobenzene (**2i**)	1.5	**3i**	59
11	**1d**	2-Bromoacetophenone (**2j**)	0.5	**3j**[h]	76
12	**1d**	2-Bromonitrobenzene (**2k**)	1	**3k**[i]	65
13	**1b**	1-Bromonaphthalene (**2l**)	1.5	**3l**	85
14	**1d**	**2l**	1.5	**3m**	96
15	**1c**	3-Bromoquinoline (**2m**)	1.5	**3n**	48

[a] All reactions were carried out using aryl halide (0.5 mmol) and arylgermanium trichloride (0.6 mmol) in dioxane (4 mL) and water (4 mL) at reflux in the presence of $Pd(OAc)_2$ (5 mol %), and NaOH (4.8 mmol).

[b] Isolated yields based on the aryl bromide.

[c] Ref.[14]

[d] Ref.[15]

[e] Ref.[16]

[f] Ref.[17]

[g] Ref.[18]

[h] Ref.[19]

[i] Ref.[20]

alities such as ketone, trifluoromethyl, and nitro groups survived the reaction, provided that it could be terminated in a short period of time (runs 5, 7–12). Aryl bromides with an *ortho*-substituent were also amenable (runs 11–14).

As for hypervalent organotin trichloride reactions,[8c,13] an active germanium species is assumed to be a hypervalent species with germanium-oxygen bonds, such as $Na_n[ArGe(OH)_{3+n}]$ (n = 1 or 2). Although the generation of these species takes only 4 or 5 equivs. (or 5 or 6 equivs. considering the structure of the germanium by-product) of sodium hydroxide, the reaction required 8 equivs. The role of the excess base may be to drive the reversible formation of the active hypervalent species to a certain extent.

After our development of a tricarbagermatran reagent,[4a] Oshima[4b] and Faller[4c] reported more easily accessible reagents. The present results suggest that the even more readily available arylgermanium trichloride, which is also a precursor of the Faller's reagent, is a useful arylating agent for palladium-catalyzed cross-coupling with aryl iodide and bromides in high yields. The reaction leaves a wide variety of functionalities intact. Since the reaction is composed of quite simple components, it does not produce any annoying by-product like the corresponding aryltrialkyltin and many arylsilicon reactions do. Thus recycle of an expected simple inorganic germanium species formed along the reaction may be feasible. The possibility of this recycle and the development of more efficient germanium reagents are under investigation.

Experimental Section

p-Anisyltrichlorogermane (1d); Typical Procedure for the Preparation of Aryltrichlorogermanes

A mixture of *p*-bromoanisole (28.3 g, 151 mmol), $GeCl_2 \cdot$dioxane complex (3.5 g, 15 mmol),[9] and anhydrous $AlCl_3$ (0.10 g, 0.75 mmol) was stirred at 80 °C for 20 h. After the mixture had cooled to room temperature, it was filtered, the volatiles were removed under vacuum, and the unreacted *p*-bromoanisole was removed by bulb-to-bulb distillation under reduced pressure. To the residual oil was added 2 M NaOH (23 mL) and the mixture was well stirred at room temperature to give a white suspension. The water was distilled off. The white solid mass thus obtained was dried at 140 °C/0.1 torr for 3 h. After cooling down to room temperature, concentrated hydrochloric acid (40 mL) was added to the product. After stirring for 3 h at room temperature, the product was extracted with dichloromethane (30 mL × 2). The extracts were combined and dried over anhydrous sodium sulfate. The title product was obtained by distillation (bp 83 °C/0.7 torr). The characterization data for compound **1d** are in the Supporting Information file.

4-Methoxy-4′-(*N*,*N*-dimethylamino)biphenyl (3b); Typical Procedure for the Cross-Coupling Reaction

In a 30-mL, two-necked, round-bottomed flask furnished with a reflux condenser and septum, *p*-anisyltrichlorogermane 0.172 g (0.6 mmol) was added to a solution composed of dioxane (4 mL), 2 M NaOH (2.4 mL), and water (1.6 mL) over 3 minutes at room temperature under an argon atmosphere. A white precipitate appeared upon the addition, which was dissolved completely within several more min. Then, 4-bromo-*N*,*N*-dimethylaniline (0.100 g, 0.5 mmol) was added dropwise, and palladium(II) acetate (0.001 g, 0.025 mmol) was added to the resulting yellow-colored solution. The yellow solution was heated under reflux for 0.5 h. After the mixture had cooled to room temperature, the precipitate formed was filtered off and the filtrate was extracted with ether (20 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate. Silica gel column chromatography after concentration afforded **3b**; yield: 0.075 g (0.33 mmol, 66%). The characterization data for compounds **3** are in the Supporting Information file.

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References

[1] a) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; b) T. N. Mitchell, in: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), VCH, Weinheim, **1998**, pp. 167–202; c) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, 1–652; d) M. Kosugi, K. Fugami, in: *Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), Wiley, New York, **2002**, pp. 263–283; e) K. Fugami, M. Kosugi, *Top. Curr. Chem.* **2002**, *219*, 87–130.

[2] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) A. Suzuki, in: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), VCH, Weinheim, **1998**, pp. 49–97; c) A. Suzuki, in: *Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), Wiley, New York, **2002**, pp. 249–262; d) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11–59; e) A. Suzuki, *Modern Arene Chem.* **2002**, 53–106.

[3] a) Y. Hatanaka, T. Hiyama, *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 834–843; b) T. Hiyama, in: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), VCH, Weinheim, **1998**, pp. 421–453; c) T. Hiyama, E. Shirakawa, in: *Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), Wiley, New York, **2002**, pp. 285–309; d) T. Hiyama, E. Shirakawa, *Top. Curr. Chem.* **2002**, *219*, 61–85; e) S. E. Denmark, M. H. Ober, *Aldrichimica Acta*, **2003**, *36*, 75–85.

[4] a) M. Kosugi, T. Tanji, Y. Tanaka, A. Yoshida, K. Fugami, M. Kameyama, T. Migita, *J. Organomet. Chem.* **1996**, *508*, 255–257; b) T. Nakamura, H. Kinoshita, H. Shinokubo, K. Oshima, *Org. Lett.* **2002**, *4*, 3165–3167; c) J. W. Faller, R. G. Kultyshev, *Organometallics* **2002**, *21*, 5911–5918; d) J. W. Faller, R. G. Kultyshev , J. Parr, *Tetrahedron Lett.* **2003**, *44*, 451–453.

[5] K. Fugami, S. Ohnuma, M. Kameyama, T. Saotome, M. Kosugi, *Synlett* **1999**, 63–64.

[6] K. Fugami, M. Kameyama, M. Kosugi, *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 769–777.

[7] a) P. Riviere, M. Riviere-Baudet, J. Satgè, in: *Comprehensive Organometallic Chemistry*, Vol. 2, (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon Press, Oxford, **1982**, pp 399–518; b) R. Laurent, A. Laporterie, J. Dubac, J. Berlan, *Organometallics* **1994**, *13*, 2493–2495; c) M. Massol, P. Piviere, *J. Organomet. Chem.* **1973**, *56*, 1–39; d) S. P. Kolesnikov, B. L. Perlmutter, O. M. Nefedov, *Dokl. Alad. Nauk SSSR* **1971**, *196*, 594–596; *Doklady Chem.* **1971**, 85–88; e) K. Kuhlein, W. P. Neumann, *Liebigs Ann. Chem.* **1967**, *702*, 17–23; f) D. Seyferth, J. Hetflejs, *J. Organomet. Chem.* **1968**, *11*, 253–261; g) F. Riedmiller, G. L. Wegner, A. Jockisch, H. Schmidbaur, *Organometallics* **1999**, *18*, 4317–4324; h) O. H. Johnson, D. M. Harris, *J. Am. Chem. Soc.* **1950**, *72*, 5564–5566; i) A. El-Maradny, H. Tobita, H. Ogino, *Organometallics* **1996**, *15*, 4954–4958.

[8] a) A. I. Roshchin, N. A. Bumagin, I. P. Beletskaya, *Tetrahedron Lett.* **1995**, *36*, 125–128; b) R. Rai, K. B. Aubrecht, D. B. Collum, *Tetrahedron Lett.* **1995**, *36*, 3111–3114; c) N. A. Bumagin, A. I. Roshchin, *Zh. Obshch. Khim.* **2000**, *70*, 61–68; *J. Gen. Chem.* **2000**, *70*, 57–63.

[9] a) A. C. Spivey, C. M. Diaper, A. J. Rudge, *Chem. Commun.* **1999**, 835–836; b) A. C. Spivey, C. M. Diaper, H. Adams, *J. Org. Chem.* **2000**, *65*, 5253–5263; c) T. Fjeldberg, A. Haaland, B. E. R. Schilling, M. F. Lappert, A. J. Thorne, *J. Chem. Soc. Dalton Trans.* **1986**, 1551–1556; d) V. F. Mironov, T. K. Gar, *J. Gen. Chem. USSR* **1975**, *45*, 94–98; e) I. P. Shcherbinin, K. V. Shevedov, K. V. Pavlov, N. G. Komalenkova, E. A. Chernyshev, *Russ. J. Gen. Chem.* **1998**, *68*, 1013–1016.

[10] a) W. R. Orndorff, D. L. Tabern, L. M. Dennis, *J. Am. Chem. Soc.* **1927**, *49*, 2512–2516; b) E. A. Flood, *J. Am. Chem. Soc.* **1933**, *55*, 4935–4938; c) O. H. Johnson, L. V. Jones, *J. Org. Chem.* **1952**, *17*, 1172–1176; d) E. A. Flood, *J. Am. Chem. Soc.* **1932**, *54*, 1663–1667; e) H. H. Anderson, *J. Am. Chem. Soc.* **1960**, *82*, 3016–3018.

[11] T. Koike, A. Mori, *Synlett* **2003**, *12*, 1850–1852.

[12] a) A. G. Martinez, J. O. Barcina, A. de Fresno Cereso, L. R. Subramanian, *Synlett* **1994**, 1047–1048; b) E. Fouquet, M. Pereyre, A. L. Rodriguez, *J. Org. Chem.* **1997**, *62*, 5242–5243.

[13] T. Huang, Y. Meng, S. Venkatraman, D. Wang, C.-J. Li, *J. Am. Chem. Soc.* **2001**, *123*, 7451–7452.

[14] D. Zim, V. R. Lando, J. Dupont, A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049–3051.

[15] a) Y. Hatanaka, K. Goda, Y. Okahara, *Tetrahedron* **1994**, *50*, 8301–16; b) M. Ueda, A. Saitoh, S. Oh-tani, N. Miyaura, *Tetrahedron*, **1998**, *54*, 13079–13086.

[16] V. Farina, B. Krishnan, D. R. Marshall, G. P. Roth, *J. Org. Chem*. **1993**, 58, 5434–5444.
[17] H. A. Brune, B. Stapp, G. Schmidtberg, *J. Organomet. Chem*. **1986**, *307*, 129–137.
[18] D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem*. **1997**, *62*, 7170–7173.
[19] S. Darses, G. Michaud, J.-P. Genet, *Eur. J. Org. Chem*. **1999**, 1875–1883.
[20] S. E. Denmark, M. H. Ober, *Org. Lett*. **2003**, *5*, 1357–1360.