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Palladium-Catalyzed Cross-Coupling Reaction Using Arylgermanium Sesquioxide

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Abstract: Powdery reagents obtained by complete alkaline hydrolysis of arylgermanium trichlorides were found to undergo the palladium-catalyzed cross-coupling reaction with aryl bromides and iodides in good yields. The reaction is performed in an aqueous medium taking sodium hydroxide as an activator. Some base-sensitive functionalities such as acetyl and trifluoromethyl groups survived the reaction.

Keywords: biaryls; cross-coupling; germanium; palladium

The palladium-catalyzed cross-coupling reaction is a powerful synthetic tool. Various metals have been utilized as the key element of reagents. Organotin (Stille reaction)[1] and organoboron reagents (Suzuki–Miyaura reaction)[2] are particularly important because of the stability of the reagents and wide tolerance of otherwise reactive functionalities. However, there are serious drawbacks associated with each process. In the Stille reaction, a toxic by-product is generated. In the Suzuki–Miyaura reaction, organoboron reagents are not so easy to prepare and handle. Moreover, the reagent itself is toxic. Recently, organosilicon reagents (Hiyama reaction),[3] which are free from the toxicity problem, are being considered as a promising substitute for those precedents. On the other hand, the organogermanium-mediated cross-coupling reaction has scarcely been studied, while germanium lies between tin and silicon in a periodic table and organogermanium compounds are not toxic.

The first example of the organogermanium-mediated cross-coupling reaction was developed in these laboratories.[4] Very good yields were achieved using organotricarbagermatrane. The reaction is not convenient, however, owing to the laborious process necessary to prepare the reagents. Recently, Faller et al. developed an analogous reagent, arylgermatrane.[5] Oshima and co-workers reported that organotri(2-furyl)germanes act as efficient coupling reagents.[6] Although the former reagent is easy to prepare, it is not only highly toxic, but also not so high yielding. The latter reagents undergo the cross-coupling reaction in high yields. The reaction is, however, not atom-economical. These two examples both need a fluoride ion source to activate the reagents. Metal fluorides as well as ammonium fluorides are not only expensive but also toxic and contamination of fluoride ion in the waste water makes its disposal process laborious. Therefore it is preferable to avoid the use of fluoride ion reagents.

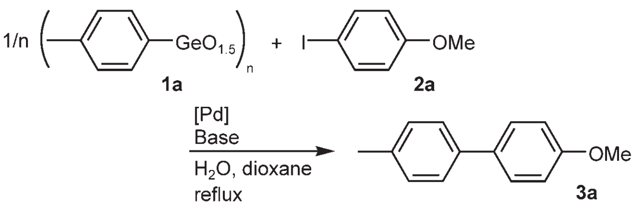
In this context, we have developed an organogermanium trichlorides-mediated cross-coupling reaction that proceeds under fluoride ion-free conditions.[7] The reagent is easily accessible, and the reaction is atom-efficient and does not emit any hazardous waste. Although organogermanium trichlorides are easier to handle than the tin and silicon counterparts, their germanium-chlorine bonds are still prone to be hydrolyzed upon exposure to moist air.

We disclose here that a crude product obtained by complete hydrolysis of arylgermanium trichloride can be used as a reagent for the palladium-catalyzed cross-coupling reaction.

The reagent can be conveniently prepared. According to Anderson's procedure,[8,9] we treated *p*-tolylgermanium trichloride with ammonia water to prepare the *p*-tolylgermanium sesquioxide (**1a**). The crude product was a non-hygroscopic white powder that was neither soluble in any organic solvent nor in water. The crude product was assumed to be **1a**, according to its elemental analysis[10] and the comparison of the IR spectra of the substrate and the crude product.[11]

We examined the Pd-catalyzed cross-coupling reaction of **1a** with *p*-iodoanisole (**2a**) (Table 1).

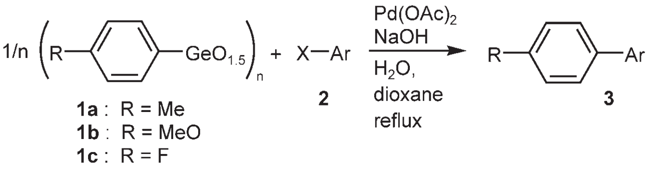
Table 1. Effects of catalyst and base on the cross-coupling of **1a** with **2a**.[a]



Run	Catalyst	Base[b] (mol equivs.)	Time [h]	Yield[c] [%]
1	Pd(OAc)$_2$	KOH (4)	4	48[d]
2	Pd(OAc)$_2$	*t*-BuONa (4)	4	49
3	Pd(OAc)$_2$	K_2CO_3 (4)	4	3[d]
4	Pd(OAc)$_2$	Cs_2CO_3 (4)	4	0
5[e]	Pd(OAc)$_2$	CsF (4)	4	23[d]
6	Pd(OAc)$_2$	NaOH (4)	4	58
7	PdCl$_2$	NaOH (4)	4	54
8	Pd(OAc)$_2$/4 tppts[f]	NaOH (4)	4	54[d]
9	PdCl$_2$/4 tppts[f]	NaOH (4)	4	57[d]
10	Pd(OAc)$_2$/dppf[g]	NaOH (4)	4	52
11	PdCl$_2$/dppf[g]	NaOH (4)	4	53
12	Pd(OAc)$_2$/2 dppp[h]	NaOH (4)	4	48
13	Pd(OAc)$_2$/2 [P][i]	NaOH (4)	24	59
14	Pd(OAc)$_2$/2 P(*n*-Bu)$_3$	NaOH (4)	4	53
15	Pd(OAc)$_2$/2 P(*o*-tolyl)$_3$	NaOH (4)	24	21
16	Pd(OAc)$_2$/2 P(mesityl)$_3$	NaOH (4)	24	11
17	Pd(OAc)$_2$/2 P(cyclohexyl)$_3$	NaOH (4)	4	9[d]
18	PdCl$_2$/2 P(cyclohexyl)$_3$	NaOH (4)	4	18[d]
19	Pd(OAc)$_2$[j]	NaOH (4)	4	51
20	Pd(OAc)$_2$[k]	NaOH (4)	4	52
21	Pd(OAc)$_2$[l]	NaOH (4)	24	34
22	Pd(OAc)$_2$[m]	NaOH (4)	4	52
23	Pd(OAc)$_2$	NaOH (3)	3	48
24	Pd(OAc)$_2$	NaOH (4)	3	56
25	Pd(OAc)$_2$	NaOH (5)	3	56
26	Pd(OAc)$_2$	NaOH (6)	3	45

[a] Reactions employed **1a** (0.6 mmol Ge), **2a** (0.5 mmol), 5 mol% of palladium, and 4 mL each of solvents.
[b] Molar equivs. to germanium.
[c] Isolated yields unless otherwise noted.
[d] Determined by VPC.
[e] DMF (8 mL) was used in place of water and dioxane.
[f] tppts = tris(3-sulfophenyl)phosphine trisodium salt.
[g] dppf = 1,1′-bis(diphenylphosphino)ferrocene.
[h] dppp = 1,3-bis(diphenylphosphino)propane.
[i] [P] = tris(2,4,6-trimethoxyphenyl)phosphine.
[j] NaCl (3.6 mmol) was used as an additive.
[k] LiCl (3.6 mmol) was used as an additive.
[l] CuI (1.2 mmol) was used as an additive.
[m] 2,6-Di-*tert*-butylphenol (1 mg) was used as an additive.

Table 2. Palladium-catalyzed cross-coupling of **1** and **2**.[a]



Run	1	2	Time [h]	Product	Yield[b] [%]
1	**1a**	4-IC$_6$H$_4$OMe (**2a**)	4	**3a**	58
2	**1a**	3-IC$_6$H$_4$OMe (**2b**)	4	**3b**	31
3	**1a**	2-IC$_6$H$_4$OMe (**2c**)	4	**3c**	16
4	**1a**	4-IC$_6$H$_4$NO$_2$ (**2d**)	1.5	**3d**	75
5	**1b**	**2d**	4	**3e**	71[c]
6	**1c**	**2d**	4	**3f**	62
7	**1b**	4-IC$_6$H$_4$CH$_3$ (**2e**)	4	**3g**	77
8	**1a**	4-BrC$_6$H$_4$OMe (**2f**)	8	**3a**	47
9	**1a**	4-BrC$_6$H$_4$NO$_2$ (**2g**)	4	**3d**	66
10	**1b**	**2g**	8	**3e**	45[c]
11	**1a**	1-Br-Naphthyl (**2h**)	4	**3h**	66[c]
12	**1b**	**2h**	1	**3i**	81
13	**1a**	4-BrC$_6$H$_4$COCH$_3$ (**2i**)	1.5	**3j**	54
14	**1b**	**2i**	1	**3k**	41
15	**1b**	3-BrC$_6$H$_4$CF$_3$ (**2j**)	1	**3l**	76[c]
16	**1b**	4-BrC$_6$H$_4$F (**2k**)	2	**3m**	58
17	**1b**	4-BrC$_6$H$_4$CH$_3$ (**2l**)	8	**3g**	51

[a] Reactions employed **1** (0.6 mmol Ge), **2** (0.5 mmol), Pd(OAc)$_2$ (5 mol%), and 4 mL each of solvents.
[b] Isolated yields unless otherwise noted.
[c] Determined by VPC.

Palladium acetate and chloride were effective as the catalyst. Strong bases such as potassium hydroxide, sodium *tert*-butoxide, and sodium hydroxide gave better results (runs 1, 2 and 6). Weaker bases such as potassium and cesium carbonates were inefficient (runs 3 and 4). Fluoride ion showed a moderate effect (run 5). Although the addition of phosphines, inorganic salts, and radical scavenger improved a number of related reactions, their effects were not obvious on the present reaction (runs 8–22). The reaction was moderately dependent on the amount of added base. Maximum yields were obtained when sodium hydroxide in 4 or 5 mol equivs. to germanium was used (runs 24 and 25). On the other hand, the yields decreased with higher or lower amounts of the base (runs 23 and 26).

We next examined a variety of combinations between **1** and aryl halide **2** under the conditions of run 6 in Table 1. The results are summarized in Table 2.

Not only aryl iodides but also bromides reacted to afford the corresponding biaryls in moderate to good yields. Although the reaction was sensitive to steric hindrance (runs 1–3), aryl halides with electron-donating as well as -withdrawing substituents gave good yields. It is worth noting that base-sensitive functionalities such as ketone and trifluoromethyl groups survived the reaction (runs 13–15).

In conclusion, easily accessible arylgermanium sesquioxides are found to exhibit a good reactivity toward the palladium-catalyzed cross-coupling reaction with a variety of aryl halides without taking any toxic or expensive additives. Since the germanium reagents are also non-toxic, the process is environmentally benign. These aspects in combination with the reagent's robustness under ambient conditions will offer a new approach to the utilization of organogermaniums. Since the reaction is composed of simple components, recycle of an expected simple inorganic germanium species formed along the reaction is feasible. Development of a recycling process for germanium is under investigation.

Experimental Section

Typical Procedure for the Cross-Coupling Reaction

In a 30-mL two-necked, round-bottomed flask furnished with a reflux condenser, magnetic stirring bar, and a rubber septum, *p*-tolylgermanium sesquioxide (113 mg, 0.6 mmol) was added to a solution composed of dioxane (4 mL), aqueous NaOH solution (2.0 mol dm^{-3}, 1.2 mL, 2.4 mmol), and water (2.8 mL) at room temperature under an argon atmosphere. The resulting white suspension was stirred for 10 min to dissolve the precipitate to give a clear solution. Then, *p*-iodoanisole (**2a**, 117 mg, 0.5 mmol) and palladium(II) acetate (5.6 mg, 0.025 mmol) were added. The resulting yellow solution was heated to reflux for 4 h. After the mixture was cooled to room temperature, the products were extracted with dichloromethane (20 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate. Silica-gel column chromatography after concentration afforded 4-methoxy-4′-methylbiphenyl (**3a**);[12] yield: 57 mg (58%).

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[10] Detailed procedure and elemental analyses data of the products are presented in the Supporting Information.

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