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Biaryl Synthesis from Two Different Aryl Halides with Tri(2-furyl)germane

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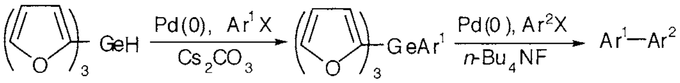
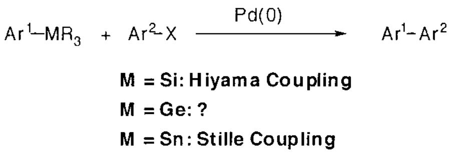
ABSTRACT



The coupling reaction of germanium compounds with aryl halides has been developed. The Pd(0)-catalyzed reaction of aryl halides with tri(2-furyl)germane provides aryltri(2-furyl)germanes in good yield. The cross-coupling reaction of aryltri(2-furyl)germanes with aryl halides is acheived. This allows facile synthesis of unsymmetrical biaryls from two different aryl halides.

Group 14 metals are popular key elements among a number of cross-coupling reactions between organometallic compounds and organic halides under Pd(0) catalysis (Scheme 1).[1] The Stille coupling is particularly important because of its mild reaction conditions and wide functional compatibility.[2] Since Denmark and Mori independently have found that coupling with silanols proceeds under milder conditions than Hiyama's original procedure,[3] the Hiyama coupling has received increasing attention due to the stability and low toxicity of silicon compounds.[4] However, despite the wide application of these two coupling methods, coupling with organogermanes has been scarcely explored so far, although germanium is located between silicon and tin in a periodic table.[5]

Scheme 1. Coupling Reactions with Group 14 Metals



Recently, we have investigated unique properties of tri(2-furyl)germyl compounds.[6] We have also devoted our effort to develop an efficient coupling reaction with arylgermanes to bridge the apparent gap between arylsilanes and arylstannanes in the cross-coupling chemistry. Herein, we wish to report the cross-coupling reactions between aryltri(2-furyl)germanes and aromatic halide in the presence of a Pd(0) catalyst. Aryltri(2-furyl)germanes are readily accessible from aryl halides and tri(2-furyl)germane, and this allows facile synthesis of unsymmetrical biaryls from two different aryl halides.

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[1] *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.

[2] Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1998.

[3] (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (c) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (d) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495. (e) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (f) Denmark, S. E.; Wang, Z. *Synthsis* **2000**, 999. (g) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (h) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266.

[4] Hatanaka, Y.; Hiyama, T. *Pure Appl. Chem.* **1994**, *66*, 1471.

[5] Only one example of the coupling with germatranes has been reported; see: Kosugi, M.; Tanji, T.; Tanaka, Y.; Yoshida, A.; Fugami, K.; Kameyama, M.; Migita, T. *J. Organomet. Chem.* **1996**, *508*, 255. The scope and limitations have not been investigated.

[6] (a) Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 4220. (b) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 747. (c) Tanaka, S.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 1911. (d) Kinoshita, H.; Nakamura, T.; Kakiya, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 2521. (e) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 9827. (f) Nakamura, T.; Tanaka, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *C. R. Acad. Sci. Paris, Chim.* **2001**, *4*, 461.

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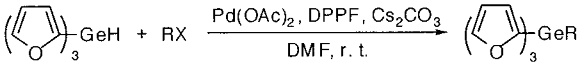
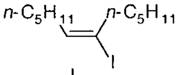
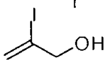
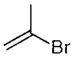
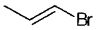
Table 1. Palladium-Catalyzed Germylation of Aryl or Vinyl Halides[a]



1 **2**

entry	RX	time (h)	product	yield (%)
1	PhI	1.5	**2a**	83
2	4-MeOC$_6$H$_4$I	1	**2b**	80
3	3-MeOC$_6$H$_4$I	1	**2c**	88
4	4-MeC$_6$H$_4$I	0.5	**2d**	85
5	2-MeC$_6$H$_4$I	2	**2e**	43
6	4-Me$_2$NC$_6$H$_4$I	1	**2f**	56
7		0.5	**2g**	83
8		3	**2h**	59
9	4-MeOC$_6$H$_4$Br	12	–	0
10		1.5	**2i**	70
11		1	**2j**	54
12	α-Bromostyrene	1	**2k**	49
13	(*E*)-β-Bromostyrene	1.5	**2l**	74
14	2-Bromopyridine	2	**2m**	73

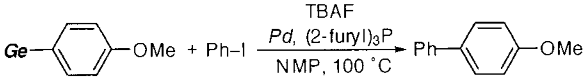
[a] Tri(2-furyl)germane (1.0 mmol), RX (1.2 mmol), Pd(OAc)$_2$ (0.050 mmol), DPPF (0.050 mmol), Cs$_2$CO$_3$ (1.1 mmol), and DMF (10 mL) were employed.

We examined the coupling reaction of tri(2-furyl)germane (**1**) with a variety of aryl iodides.[7] To a mixture of Pd$_2$(dba)$_3$•CHCl$_3$ (0.025 mmol), tri(2-furyl)phosphine (0.10 mmol), and Cs$_2$CO$_3$ (1.1 mmol) in DMF were sequentially added tri(2-furyl)germane (**1**) (1.0 mmol) and iodobenzene (1.2 mmol) at room temperature. The mixture was stirred for 1 h. Aqueous workup and purification afforded arylgermane **2a** in 61% yield. After extensive optimization of the reaction conditions, we found that a Pd(OAc)$_2$/DPPF/Cs$_2$CO$_3$ combination was particularly effective and improved the yield of **2a** up to 83%. In the absence of a ligand or a base, the desired product was not obtained at all. It is striking that the reaction of 4-iodoanisole provided a trace amount of anisole, while the analogous reaction with Et$_3$SiH[8] or *n*-Bu$_3$SnH[9] resulted in the formation of anisole via the reduction of halide.

Table 1 summarizes the results of germylation of aryl and alkenyl halides under the optimized reaction conditions. Electron-rich aryl iodides such as iodoanisoles and 4-iodotoluene afforded the corresponding arylgermanes in good yields (Table 1, entries 2–4). The use of 2-iodotoluene lowered the yield of the coupling product probably due to the steric hindrance at the ortho position (Table 1, entry 5). Not only aryl iodides but also vinyl halides can be employed (Table 1, entries 7 and 8). Disappointingly, aryl bromide did not undergo coupling (Table 1, entry 9). In contrast, vinyl bromides and 2-bromopyridine furnished the corresponding products in moderate to good yields (Table 1, entries 10–14).

We then turned our attention toward the cross-coupling reaction of aryltri(2-furyl)germanes with aryl halides. After extensive investigation of the reaction conditions, we found that an addition of fluoride induced the cross-coupling of 4-methoxyphenylgermane **2b** with aryl halides (Table 2). The amount of TBAF was crucial for the successful coupling. To obtain the desired biaryl in satisfactory yield, more than 4.0 equiv of TBAF was required (Table 2, entries 1–5). As the palladium source, Pd$_2$(dba)$_3$•CHCl$_3$ proved to be the best (Table 2, entry 7).

Table 2. Cross-Coupling Reaction with Iodobenzene[a]



2b ***Ge*** = (2-furyl)$_3$Ge **3a**

entry	Pd	TBAF[b] (equiv)	time (h)	yield (%)
1	Pd(OAc)$_2$	1.2	5	0
2	Pd(OAc)$_2$	2.4	10	23
3	Pd(OAc)$_2$	3	5	52
4	Pd(OAc)$_2$	4	5	77
5	Pd(OAc)$_2$	5	5	81
6[c]	Pd(OAc)$_2$	5	10	0
7	Pd$_2$(dba)$_3$•CHCl$_3$	4	5	90

[a] Arylgermane **2b** (1.0 mmol), PhI (1.2 mmol), Pd(OAc)$_2$ (0.020 mmol), or Pd$_2$(dba)$_3$•CHCl$_3$ (0.010 mmol), (2-furyl)$_3$P (0.020 mmol), and NMP (10 mL) were employed. [b] 1.0 M THF solution. [c] The reaction was carried out at 60 °C.

The key of this coupling process is the use of the tri(2-furyl)germyl group. It is noteworthy that none of the coupling reaction proceeded with Ph$_4$Ge under numerous reaction conditions with or without fluoride. To obtain mechanistic insights of this process, we examined the reaction of an aryltri(2-furyl)germane with TBAF. Arylgermane **2b** was treated with 4.0 equiv of TBAF in THF at reflux for 5 h. After solvent was removed, ^{1}H and ^{13}C NMR spectra of the residue indicated the presence of a 4-methoxyphenyl group but not furyl groups. In the ^{9}F NMR, no other peaks than TBAF were detected. These observations indicate that all three furyl groups on germanium were cleaved with fluoride to form ArGe(OH)$_3$ or germanoxanes.[10] We speculate that

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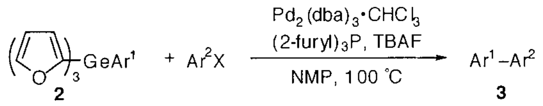
(7) Coupling between aryl and alkenyl halides and HSi(OEt)$_3$ has been reported. Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569; Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **1999**, *40*, 9255. A Pd-catalyzed coupling of aryl iodide with Bu$_3$SnH via formation of Bu$_3$SnSnBu$_3$ has been reported. Murata, M.; Watanabe, S.; Masuda, Y. *Synlett* **2000**, 1043.

(8) Boukherroub, R.; Chatgilialoglu, C.; Manuel, G. *Organometallics* **1996**, *15*, 1508.

(9) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.

(10) Fluoride-induced cleavage of Si–heteroaryl bonds: (a) Itami, K.; Mitsudo, K.; Yoshida, J. *J. Org. Chem.* **1999**, *64*, 8709. (b) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577.

Table 3. Cross-Coupling of Aryltri(2-furyl)germane with Aryl Halides[a]



entry	Ar^1	Ar^2X	time (h)	product	yield (%)
1	4-$MeOC_6H_4$ **2b**	PhI	5	**3a**	90
2	**2b**	PhBr	6.5	**3a**	100
3	**2b**	3-$CF_3C_6H_4Br$	1	**3b**	80
4	**2b**	1-iodonaphtalene	4	**3c**	70
5	**2b**	3-$MeOC_6H_4I$	2	**3d**	59
6	**2b**	4-MeC_6H_4I	1	**3e**	56
7	Ph **2a**	PhI	5	**3f**	61
8	**2a**	3-$CF_3C_6H_4Br$	9	**3g**	64
9	**2a**	1-iodonaphtalene	6	**3h**	52
10	3-$MeOC_6H_4$ **2c**	PhI	5	**3i**	59
11	**2c**	3-$CF_3C_6H_4Br$	10	**3j**	64
12	**2c**	1-iodonaphtalene	10	**3k**	65
13	(*E*)−1-Octenyl **2n**	PhI	8	**3l**	60

[a] Arylgermane **2** (1.0 mmol), Ar^2X (1.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.010 mmol), $(2\text{-furyl})_3P$ (0.020 mmol), TBAF (4.0 mmol), and NMP (10 mL) were employed.

nucleophilic hypervalent oganogermanium species such as $[ArGe(OH)_3F]^-$ undergo transmetalation from germanium to palladium.

Table 3 summarizes the results of the cross-coupling reaction with a variety of aryl halides.[11] Aryl bromides as well as aryl iodides afforded the desired products in good yields (Table 3, entries 1 and 2). Electron-donating groups on aryl halides slightly lowered the yields of biaryls (Table 3, entries 5 and 6). Treatment of aryl or vinyl germanes (**2a**, **2c**, and **2n**) with aryl halides yielded the corresponding biaryls or styrenes in moderate yields (Table 3, entries 7−13). In all cases, none of furylated products were observed.

In summary, we have achieved the coupling reaction between tri(2-furyl)germane and aryl halides providing aryltri(2-furyl)germanes, which can be further cross-coupled with a variety of halides under Pd(0) catalysis. This new protocol enables the facile synthesis of unsymmetrical biaryls from two different aryl halides.

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Supporting Information Available: General procedures and spectral data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We have attempted the synthesis of unsymmetrical biaryls in a one-pot operation. Tri(2-furyl)germane was treated with 4-iodoanisole in the presence of $Pd(OAc)_2$, DPPF, and Cs_2CO_3 in DMF. After 1 h, iodobenzene, TBAF, and NMP were added, and then the mixture was heated at 100 °C for 10 h. 4-Methoxybiphenyl **3a** was obtained in 34% yield.