ORGANIC LETTERS

1999
Vol. 1, No. 9
1495−1498

Synthesis of Unsymmetrical Biaryls from Arylsilacyclobutanes

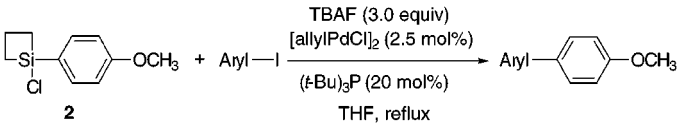
Scott E. Denmark* and Zhicai Wu

Roger Adams Laboratory, Department of Chemistry, University of Illinois, 600 South Mathews Avenue Urbana, Illinois 61801

denmark@scs.uiuc.edu

Received September 15, 1999

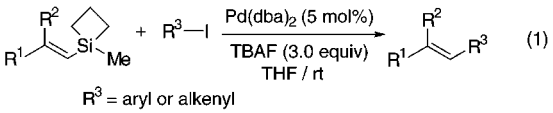
ABSTRACT



Aryl(fluoro)silacyclobutanes and aryl(chloro)silacyclobutanes have been found to undergo cross-coupling reactions with aryl iodides. The rate of reaction and extent of homocoupling were dramatically affected by the addition of ligands for the palladium catalyst. With (*t*-Bu)$_3$P a wide range of electronically and structurally diverse unsymmetrical biaryls have been prepared in good to excellent yields.

The biaryl subunit is a commonly found motif in biologically active molecules.[1] Moreover, biaryl-containing compounds can be used to design novel materials such as organic semiconductors and liquid crystals.[2] Accordingly, the construction of biaryls remains an active area in organic synthesis.[3] Transition metal-catalyzed cross-coupling reactions between arylmetallic nucleophiles and aryl electrophiles, disclosed by the Kumada−Tamao[4] and the Corriu groups,[5] have had a revolutionary impact on the preparation of biaryls.[6] Among the most notable and widely used are the Stille (Migita−Kosugi) coupling of organostannanes[7] and Suzuki coupling of organoboranes.[8] These two methods have the common advantages of high yields and selectivities and applying stable, isolable entities. However, they are not without disadvantages such as attenuated and substrate-dependent reactivity, oxygen sensitivity, and toxicity.

Organosilicon reagents can, in principle, provide a practical solution to these problems because they are environmentally benign and stable to many reaction conditions. Despite their lower reactivity, acyclic aryl(fluoro)silanes have been shown through the extensive studies by Hiyama group to participate in the palladium-catalyzed cross-coupling reactions including preparing biaryls.[9] Alkoxysilanes[10] and silanols[11] have also been demonstrated as appropriate coupling partners. Recently, we have introduced the use of alkenylsilacyclobutanes for highly stereospecific cross-coupling reactions (eq 1).[12]



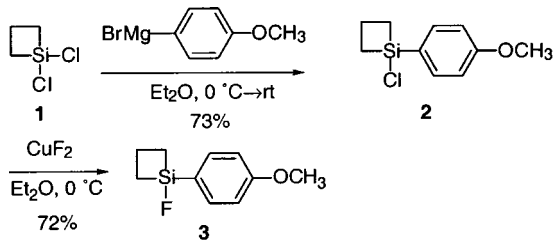
(1) (a) Torssell, K. G. B. *Natural Product Chemistry*; Wiley: Chichester, 1983. (b) Thomson, R. H. *The Chemistry of Natural Products*; Blackie and Son: Glasgow, 1985.
(2) (a) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (b) Yamamura, K.; Ono, S.; Ogoshi, H.; Masuda, H.; Kuroda, Y. *Synlett* **1989**, 18.
(3) (a) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (b) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl*. **1990**, *29*, 977. (c) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327.
(4) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc*. **1972**, *94*, 4374.
(5) Corriu, R. J. P.; Masse, J. P. *Chem. Commun*. **1972**, 144.
(6) (a) Dielderich, F., Stang, P. J., Eds. *Metal-Catalyzed, Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (c) Tsuji, I. *Palladium Reagents and Catalysis. Innovations in Organic Synthesis*; Wiley: Chichester, U.K., 1995.
(7) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React*. **1998**, *50*, 1.
(8) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457.
(9) (a) Hiyama, T. In *Metal-Catalyzed, Cross-Coupling Reactions*; Dielderich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471.
(10) (a) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun*. **1997**, 1309. (b) Mowery, M. E.; Deshong, P. *J. Org. Chem*. **1999**, *64*, 1684.
(11) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett*. **1999**, *1*, 299.
(12) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc*. **1999**, *121*, 5821.

10.1021/ol991054k CCC: $18.00
Published on Web 09/30/1999

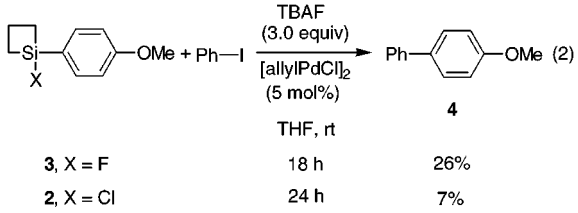
Compared to the other metal reagents, the methyl organosilacyclobutanes have the advantages of (1) low molecular weight, (2) ease of synthesis, (3) stability, (4) mild activation, and (5) conversion to harmless byproducts. To expand the scope of this method, we report herein the application of arylsilacyclobutanes for the synthesis of unsymmetrical biaryls.

Initial studies on the cross-coupling reaction of methyl(phenyl)silacyclobutane with either aryl or alkenyl iodides gave no desired products under various conditions including those optimized for alkenylsilacyclobutanes. Thus, to enhance the reactivity of the arylsilacyclobutanes, a heteroatom was introduced on the silicon. Chlorosilane **2** and fluorosilane **3** were prepared in a straightforward fashion from dichlorosilacyclobutane (**1**)[13], Scheme 1.

Scheme 1

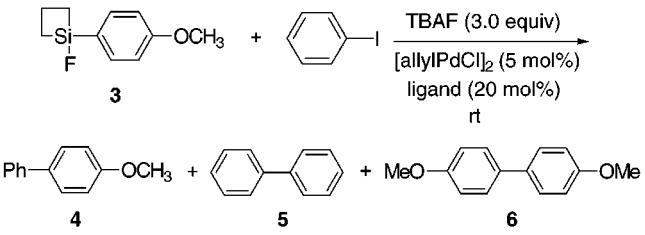


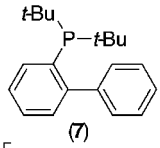
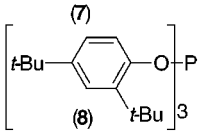
Orienting experiments with **3** and iodobenzene revealed that under standard[12] coupling conditions (TBAF/Pd(dba)$_2$/THF/rt), 25% conversion could be obtained in 48 h. Screening different Pd sources identified [allylPdCl]$_2$ as the superior catalyst in terms of rate and amount of side reaction. With this catalyst, fluorosilane **3** was found to be more reactive than chlorosilane **2** (eq 2) and thus was used to optimize the other reaction variables.



Careful investigation of the reaction between **3** and iodobenzene showed that homocoupling of both these substrates was a serious liability (entry 1, Table 1).[9b,14] To facilitate the transmetalation and eliminate the cross-coupling, various additives were surveyed with ratio of ligand/palladium of 2.0. The additives examined cover a wide range of donor properties and steric bulk. While (*o*-tol)$_3$P (entry 2), (C$_6$F$_5$)$_3$P (entry 3), and phosphite **8** (entry 9) suppressed

Table 1. The Effect of Additive on the Coupling with **3** at Room Temperature



entry	ligand	time (h)	conversion (%)	product ratio (**4** : **5** : **6**)
1	—	68	100	71 : 15 : 13
2	(*o*-tol)$_3$P	46	0	
3	(C$_6$F$_5$)$_3$P	24	0	
4	(furyl)$_3$P	46	100	86 : 14 : 0
5	Ph$_3$As	96	100	93 : 7 : 0
6	(*t*-Bu)$_3$P	90	78	73 : 5 : 0
7	(*c*-Hex)$_3$P	72	100	91 : 9 : 0
8	 (**7**)	48	100	75 : 25 : 0
9	 (**8**)	24	16	8 : 8 : 0
10	DMPE	24	85	74 : 11 : 0

the desired coupling, the other ligands such as tri(2-furyl)phosphine (entry 4) and triphenylarsine (entry 5) and the bulky ligands such as tri(*tert*-butyl)phosphine (entry 6)[15] and tricyclohexylphosphine (entry 7) were effective in eliminating the homocoupling of arylsilanes and significantly suppressing the homocoupling of aryl iodides. Nevertheless, the desired cross-coupling was still rather sluggish. It was surprising that recently introduced ligand **7** did not inhibit the generation of **5**.[16]

To accelerate the cross-coupling process, the reaction temperature was increased to 50 °C. Again, a variety of ligands were surveyed, and the results are collected in Table 2. With the exception of P(C$_6$F$_5$)$_3$ (entry 2) and DMPE (entry 5), all the other ligands allowed the reaction to be complete in 24 h. As is evident from Table 2, the ligands have a dramatic effect on the generation of homocoupling product **5**. Tri(*tert*-butyl)phosphine was the best ligand to suppress this side reaction; only 6% of **5** was produced (entry 7).

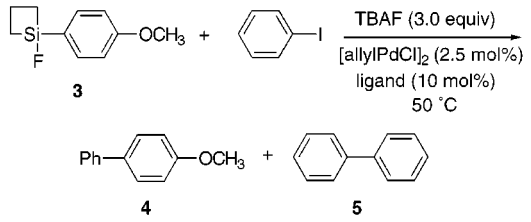
(13) Available from Aldrich or Gelest. See also: (a) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026. (b) Laane, J. *J. Am. Chem. Soc.* **1967**, *89*, 1144.

(14) Ikeyashira, K.; Nishihara, Y.; Hirabayashi, K.; Mori, A.; Hiyama, T. *J. Chem. Soc., Chem. Commun.* **1997**, 1039.

(15) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387.

(16) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

Table 2. The Effect of Additive for the Coupling with **3** at 50 °C



entry	ligand	time (h)	comversion (%)	product ratio (**4** : **5**)
1	$(o\text{-tol})_3P$	22	100	88 : 12
2	$(C_6F_5)_3P$	24	0	
3	DPPE	22	100	87 : 13
4	DPPF	22	100	50 : 50
5	DMPE	24	0	
6	$(c\text{-Hex})_3P$	22	100	75 : 25
7	$(t\text{-Bu})_3P$	22	100	94 : 6

To further reduce the amount of **5**, the ligand/Pd ratio was examined with most effective additive tri(*tert*-butyl)phosphine. As is apparent from Table 3, the more ligand added, the less **5** generated. However, the desired cross-coupling reaction was also retarded by the ligand. When the ligand/Pd ratio was over 4.2, the reaction was not complete in 22 h. Thus, the preferred ratio of (*tert*-Bu)$_3$P/Pd is 2.0 for the coupling of fluorosilane **3** with aryl iodides at 50 °C.

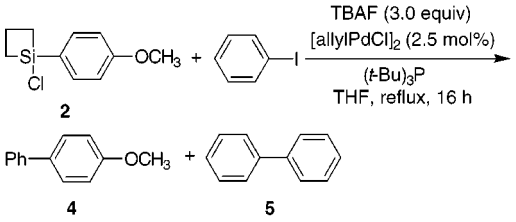
Table 3. The Effect of Ligand/Pd Ratio on the Coupling with **3**[a]

entry	$(t\text{-Bu})_3P^b$	$(t\text{-Bu})_3P$/Pd	conversion (%)	**4**:**5**
1	6	1.2	100	7:1
2	10	2.0	100	12:1
3	21	4.2	57	56:1
4	36	7.2	35	1:0

[a] See Table 2 for reaction conditions. [b] Mole % $(t\text{-Bu})_3P$ with respect to **3**.

Although our preliminary studies found fluorosilane **3** to be superior to chlorosilacyclobutane **2**, we felt that our better understanding of reaction variables now warranted a re-investigation of this reagent. Under the identical conditions noted above in Table 3, the reaction was not complete within 22 h. By carrying out the reaction in refluxing THF, complete conversion could be observed within 16 h (Table 4). However, at the elevated temperature, the amount of side product **5** increased to 11% with a $(t\text{-Bu})_3P$/Pd ratio of 2.2. We were pleased to find that amount of **5** can be reduced to less than 5% when the ratio of P(t-Bu)$_3$/Pd was increased to 4.0.

Table 4. The Effect of Ligand/Pd Ratio on the Coupling with **2**



$(t\text{-Bu})_3P$	$(t\text{-Bu})_3P$/ Pd	**4** : **5**
11 mol%	2.2	89 : 11
16 mol%	3.2	92 : 8
20 mol%	4.0	95 : 5

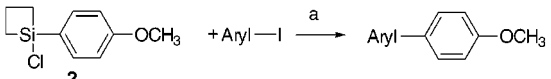
From the foregoing studies it is apparent that both chlorosilane **2** and fluorosilane **3** are appropriate partners for the cross-coupling with aryl iodides. The fluorosilane is more reactive and can perform the coupling at slightly lower temperature and with less additive. On the other hand, the chlorosilane can be easily prepared in one step. With an eye toward practicality, we selected the more readily available aryl(chloro)silacyclobutanes to demonstrate this scope of this new method.

Optimized conditions were established as follows: pretreatment of **2** with TBAF (3.0 equiv), [allylPdCl]$_2$ (2.5 mol %) as catalyst, and tri(*tert*-butyl)phosphine (20 mol %) as ligand in refluxing THF. The reactions with a variety of aryl iodides bearing electron-withdrawing or -donating groups in the para, meta, or ortho positions were investigated to show the generality of the electrophilic component (Table 5). The desired unsymmetrical biaryls were obtained in good to excellent yields within several hours for all the aryl iodides tested. The mild reaction conditions are compatible with a wide range of functional groups including carbethoxy (entry 2), acetyl (entry 3), nitro (entry 4), and cyano (entry 5). It is noteworthy that even though the coupling is slightly slowed by ortho substituents, the reaction still goes to completion within 3 h for both 2-nitrophenyl iodide (entry 11) and 2-methylphenyl iodide (entry 10). Also, heteroaromatic iodides such as 3-iodopyridine (entry 12) are well-suited for the cross-coupling reaction.

To investigate the effect of ortho substitution at the arylsilane, aryl(chloro)silacyclobutane **9** was synthesized and its reactivity was examined with several aryl iodides (Table 6). Even though the reactions were slower than those with silane **2**, all the couplings with **9** give good yields of the corresponding biaryl compounds. Remarkably, sterically crowded 2-methyl-2′-nitrobiphenyl (entry 3) and 2,2′-dimethylbiphenyl (entry 4) can be prepared cleanly in 77% and 85% yields, respectively.

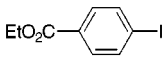
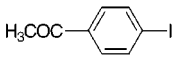
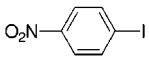
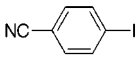
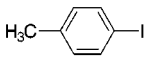
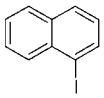
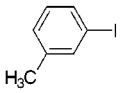
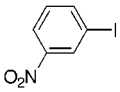
In summary, we have demonstrated the utility of hetero-substituted arylsilacyclobutanes for efficient and high-yielding cross-coupling reactions with aryl iodides. The precursors are readily prepared, stable, and storable reagents.

Table 5. Cross-Coupling of Selected Aryl Iodides with **2**



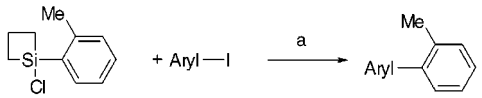
2

(a) TBAF (3.0 equiv), [allylPdCl]$_2$ (2.5 mol%), (t-Bu)$_3$P (20 mol%), THF, reflux.

entry	Aryl–I	time (h)	yield (%)
1		1	91
2		1	83
3		1	73
4		1	75
5		1	81
6		1	92
7		2	85
8		1	85
9		1	90
10		3	89
11		3	84
12		5	71

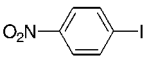
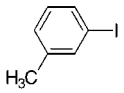
Extensive reaction optimization revealed five critical variables: (1) palladium source, (2) arylsilane, (3) additive, (4) ligand/Pd ratio, and (5) reaction temperature. The optimal conditions involve [allylPdCl]$_2$ as catalyst and (t-Bu)$_3$P as the additive. A heteroatom substituent on the silicon of arylsilacyclobutanes is needed to enhance the reactivity.

Table 6. Cross-Coupling of Selected Aryl Iodides with Aryl Silane **9**



9

(a) TBAF (3.0 equiv), [allylPdCl]$_2$ (2.5 mol%), (t-Bu)$_3$P (20 mol%), THF, reflux.

entry	Aryl–I	time (h)	yield (%)
1		2	73
2		8	76
3		3	77
4		12	85

When fluorosilanes are employed, the reaction is run at 50 °C with a ligand/Pd ratio equal to 2.0. If chlorosilanes are used, the reaction is performed in refluxing THF with a ligand/Pd ratio of 4.0. For the biaryl synthesis, these conditions are milder than the other palladium-catalyzed processes including the acyclic arylsilanes and the typical Stille and Suzuki reactions.

Extension of the scope of the silacyclobutane cross-coupling reactions and a study of the mechanistic details will be reported in due course.

Acknowledgment. Financial support was provided by the National Science Foundation (NSF CHE 9803124). Z.W. gratefully acknowledges the University of Illinois for a Graduate Fellowship.

Supporting Information Available: Preparation and full characterization of **2**, **3**, and **9** and a representative procedure for the coupling. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991054K