

An Efficient Catalyst System for Palladium(0)-Catalyzed Cross-Coupling of Aryltrialkoxysilanes with Aryl Halides

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Received: The date will be inserted once the manuscript is accepted.

Abstract: A combination of Pd(dba)₂ and a bis-phosphine ligand, bis(2-diisopropylphosphinophenyl)ether, has proven to be general and efficient in fluoride-induced cross-coupling of aryltrialkoxysilanes with aryl halides. The substrate scope is broad and includes a variety of aryl bromides and chlorides.

Key words: Silicon, Palladium, Catalysis, Cross-Coupling, Biaryls

The palladium-catalyzed cross-coupling reaction of organometallic reagents with organic electrophiles has emerged as a general and powerful method for carbon-carbon bond formation. Stille¹ and Suzuki² coupling protocols continue to be widely employed to construct biaryls that play important roles in numerous functional organic molecules. Nevertheless, the use of silicon compounds has attracted much attention as an alternative to the Stille and Suzuki coupling reactions mainly due to the formation of nontoxic by-products and stability to many reaction conditions.³ Among the various types of silicon compounds available, aryltrialkoxysilanes are more useful coupling reagents in view of availability.^{4,5} This protocol, however, lacks generality: heteroaryl or sterically hindered halides are often problematic, with undesirable homo-coupling or high catalyst loading.^{4b,c} In this paper, we wish to report a general protocol for palladium-catalyzed cross-coupling of aryltrialkoxysilanes **1** with aryl halides **2**. Our catalyst system using a bis-phosphine ligand overcomes many limitations of previous methods.

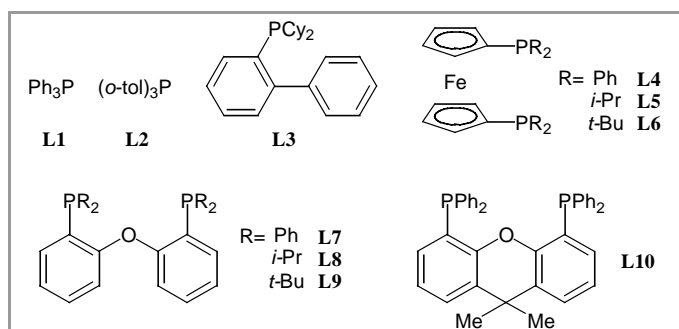


Figure 1 Phosphine ligands

An initial screen was performed using several phosphine ligands **L1–L10** (Figure 1) for the coupling reaction of phenyltrimethoxysilane (**1a**) and 4-bromoanisole (**2a**). The results are summarized in Table 1. Treatment of **2a** (1 equiv) with **1a** (1.2 equiv) and TBAF (1.2 equiv) in the presence of 3 mol% of Pd(dba)₂ and the phosphine ligand (Pd/P=1/2.7) in toluene at 80 °C was found to

lead to the cross-coupling product **3a**. This produced, in addition to the desired **3a**, side products: homo-coupled biaryl **4** and reduced arene **5**. Surprisingly, the use of mono-phosphine ligands **L1–L3**, which was known to contribute to this coupling,^{4b,c} led to the formation of significant amounts of **4** and **5** (entries 1 and 2). Since DPPF (**L4**) and DPEphos (**L7**) were excellent supporting ligands for the palladium-catalyzed cross-coupling reaction of other organometallic reagents, we then examined bis-phosphine ligands.^{6,7} While employing **L4** was more preferable than **L1–L3** for achieving higher product selectivity to afford **3a** (entry 3), further modification of the ligand was obviously necessary. Among many trials using bis-phosphine ligands, we were pleased to observe that the use of bis(2-diisopropylphosphinophenyl)ether (**L8**, *i*-Pr-DPEphos) remarkably improved the selectivity and the formation of by-products can be completely suppressed (entry 7).⁸ In addition, complete conversion of **2a** was achieved when the reaction was performed with 1.2 equiv of **1a** and TBAF, whereas the previous fluoride-induced coupling protocols utilized large excess amounts of them.^{4a-d} Unfortunately, replacement of isopropyl group of **L8** by a *tert*-butyl group in **L9** led to the formation of anisole **5**. Presumably, transmetalation of **1a** could be hindered due to the increased steric bulk.

Table 1 Screening of Ligands for Coupling of Aryltrialkoxysilanes^a

	Ligand	Yield (%)		
		3a ^b	4 ^c	5 ^b
1 ^d	L1 , PPh ₃	80	12	7
2 ^d	L2 , P(<i>o</i> -tol) ₃	85	10	9
3 ^d	L3	75	11	6
4	L4 , DPPF	81	7	3
5	L5 , DiPPF	64	4	15
6	L6 , DtBPF	61	0	16
7	L7 , DPEphos	50	12	20
8	L8 , <i>i</i> -Pr-DPEphos	93	0	0
9	L9 , <i>t</i> -Bu-DPEphos	34	0	20
10	L10 , Xantphos	80	7	5

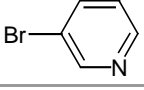
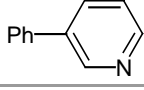
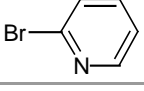
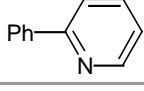
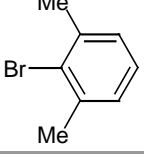
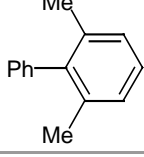
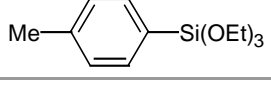
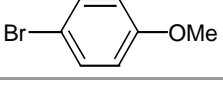
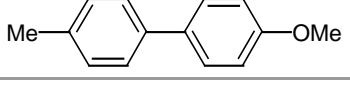
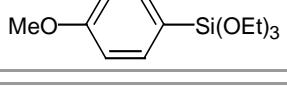
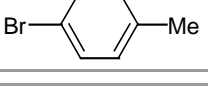
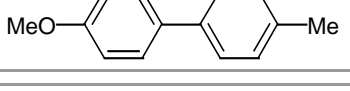
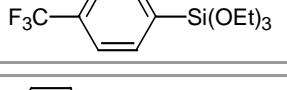
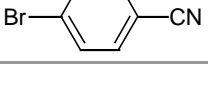
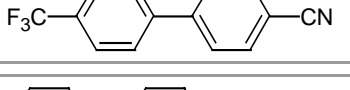
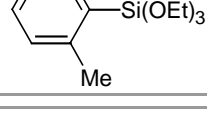
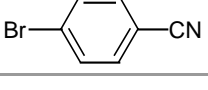
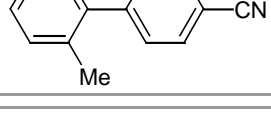
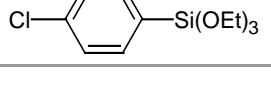
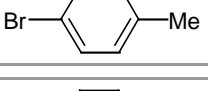
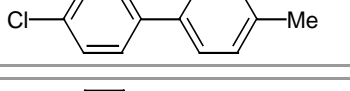
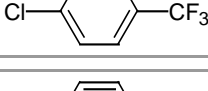
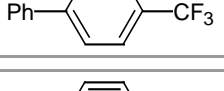
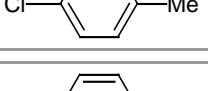
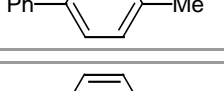
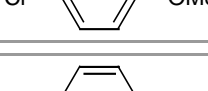
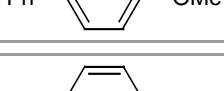
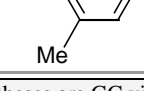
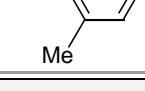
^a Reaction conditions: **2a** (0.5 mmol), **1a** (0.6 mmol), TBAF·3H₂O (0.6 mmol), Pd(dba)₂ (15 μmol), Ligand (20 μmol), in toluene (0.5 mL) at 80 °C for 4 h.

^b GC yields are based on **2a**.

^c GC yields are based on **1a**.

^d 40 μmol of phosphine ligand was used.

Table 2 Coupling Reaction of **1** with **2**

$\text{Ar-Si(OR)}_3 \quad + \quad \text{X-Ar}' \xrightarrow[\text{toluene, 80 }^\circ\text{C}]{\text{Pd(dba)}_2/\text{i-Pr-DPEphos, TBAF}} \text{Ar-Ar}'$				
Entry	ArSi(OR) ₃ 1	ArX 2	Product 3	Yield (%) ^a
1	1a			81
2	1a			73
3	1a			(85)
4				73
5				89
6				85
7				85
8				78
9 ^b	1a			93 (99)
10 ^b	1a			89 (99)
11 ^b	1a			(71)
12 ^b	1a			(62)

^a Isolated yields are based on **2a**. Yields in parentheses are GC yields.

^b The reaction was carried out at 110 °C.

After optimization of the reaction conditions, we investigated the scope of the cross-coupling of aryl halides **2** with aryltrialkoxysilanes **1**. These results are presented in Table 2. The use of the catalyst derived from Pd(dba)₂ and *i*-Pr-DPEphos **L8** demonstrated a good deal of generality, and the differences in the yields among electronic characteristics of the substituent on **1** or aryl bromides **2** (X=Br) were not particularly large. It is noteworthy that the reactions of both of heteroaryl and di-*ortho*-substituted bromides, which were problematic substrates in previous phosphine-based catalyst systems, proceeded in high yields (entries 1-3).^{4b,c} In all cases listed in Table 2, homo-coupling of neither of the reactants was detected, although small amount of reduced by-product was produced occasionally.

As aryl chlorides **2** (X=Cl) are often more readily available and less expensive than their bromide and iodide counterparts, much attention has been focused on the coupling reaction of aryl chlorides.⁹ In the fluoride-induced cross-coupling of aryltrialkoxysilanes **1**, however, high catalyst loading was required for the coupling using Buchwald's ligand system,^{4c} and *N*-heterocyclic carbenes system was not suitable for electron-neutral aryl chlorides.^{4d} Gratifyingly, the present catalyst system also proved to be highly efficient for electron-neutral and electron-deficient aryl chlorides (entries 9 and 10). In contrast, electron-donating or *ortho* substituents prevented complete conversion although nearly good to moderate yields were still obtained (entries 11 and 12).

In conclusion, we have developed a general method for cross-coupling of aryltrialkoxysilanes with aryl halides using Pd(dba)₂ / *i*-Pr-DPEphos **L8** as the catalyst. It is noteworthy that the formation of homo-coupled by-products can be almost completely suppressed. In addition, the substrate scope is significantly broader than previous methods and includes heteroaryl and sterically-hindered aryl halides. Further studies are currently underway to expand the scope of organic electrophiles.

Palladium-Catalyzed Biaryl Coupling; General Procedure (Table 2).

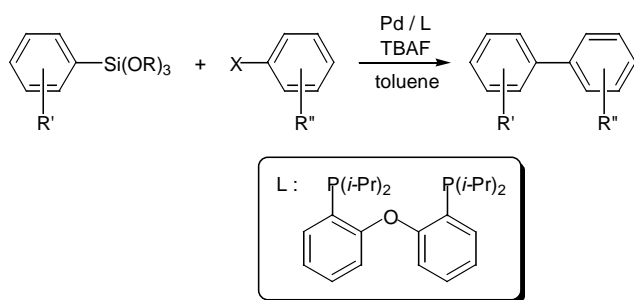
In a glove box, Pd(dba)₂ (15 μmol), *i*-Pr-DPEphos **L8** (20 μmol), and TBAF·3H₂O (0.60 mmol) were placed into a screw-capped vial, and dissolved in 0.5 mL of toluene. After being stirred for 20 min, aryl halide **2** (0.50 mmol) and aryltrialkoxysilane **1** (0.60 mmol) were added successively. The vial was sealed with a cap and removed from the glove box. The reaction mixture was then stirred at 80–110 °C for 18 h. After the reaction, the mixture was diluted with ether, washed with H₂O, and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to give the desired biaryl **3**.

Acknowledgment

This work is supported by a Grant-in-Aid for Encouragement of Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 16750069). Additional financial support by the Akiyama Foundation, and Taisho Pharmaceutical Co., Ltd. Award in Synthetic Organic Chemistry from The Society of Synthetic Organic Chemistry, Japan, is gratefully acknowledged.

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