Homocoupling of Aryl Halides Using Catalytic System of Palladium and Phosphite

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The palladium-catalyzed homocoupling of aryl halides was carried out using phosphite ligands. The optimized reaction conditions were $Pd_2(dba)_3$, phosphite **1**, and NaO*t*-Bu in diglyme, and the desired homocoupling products were afforded in moderate to good yields.

The synthesis of symmetrical biaryls has been receiving increasing research attention due to their important roles in the natural products, functional polymers, and ligands of catalyst systems.[1] These compounds are conventionally prepared by the Ullmann reaction, which involves reductive aryl halide homocoupling in the presence of stoichiometric amounts of copper reagents at high temperature (>200 °C).[2] This relatively harsh condition prevents its application in the synthesis of functionalized biaryls. Recently, various aryl metals such as aryl boronic acids,[3] arylstannanes,[4] and arylzinc[5] have been used for the synthesis of symmetric biaryls. However, they suffer the major drawback of requiring more than one equimolar amount of organometallic reagents. To address these problems, the transition-metal-catalyzed, the Ullmann-type, reductive coupling of aryl halides has been used as an alternative synthetic method. The palladium-catalyzed method has been most commonly used for the homocoupling of aryl halides. This reaction method is usually conducted in the presence of the reducing agents such as amines,[6] alcohols,[7] zinc,[8] and hydroquione.[9] As a ligand, the arylphosphines[9] or arylarsines[10] are usually employed. To our knowledge, phosphites have never been used as ligands in the palladium-catalyzed homocoupling reactions, despite their low cost and stability to air and moisture. We recently reported the Hiyama cross coupling reactions by using phosphite ligands (Figure 1).[11] In the search for the optimized condition, homocoupled aryl halide has occasionally been found as a minor constituent. Therefore, we decided to find a suitable and viable reaction method to produce a homocoupling product as the major outcome. The DeShong research group has reported a similar result in the use of tetrabutylammonium fluoride with palladium catalyst.[12] In the present study, we report an efficient homocoupling reaction involving various aryl bromides catalyzed by the palladium/phosphite system.

First, we chose 4-*tert*-butylbromobenzene as the substrate to search for the optimized condition with the palladium/phosphite system. Table 1 summarizes our results from screening a variety of palladium sources, ligands, bases and solvents. Among the ligands tested, phosphite **1** showed the best activity (Entry 1). The reactions using phosphite **2** and **3** resulted in poor yields of 47 and 40%, respectively (Entries 2 and 3). However, the single phosphadioxa cycle type lignad[13] was employed as ligand, it gave only 35% yield. Small phosphites such as $P(OEt)_3$ afforded a low yield of homocoupling product (Entry 4), while PPh_3 afforded a low yield of 35% (Entry 5). In the absence of phosphite **1**, no homocoupling products were formed and no other reactions occurred with aryl bromides under the conditions shown in Table 1 (Entry 6). Among the catalysts tested, {$Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(CH_3CN)_2Cl_2$, {Pd(allyl)Cl}$_2$, $Pd(acac)_2$}, $Pd_2(dba)_3$ proved to be the most efficient, which afforded 72% yield (Entries 1, 7, 8, 9, and 10). Palladium(0) source

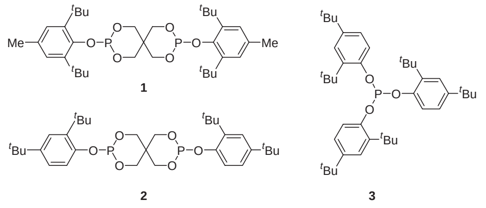
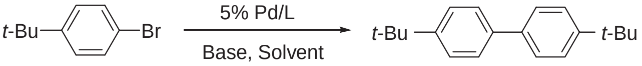


Figure 1. Phosphite ligands.

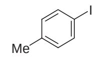
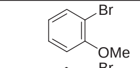
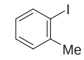
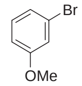
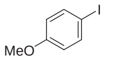
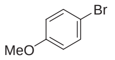
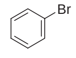
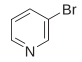
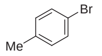
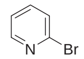
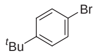
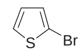
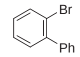
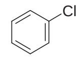
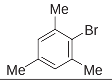
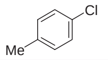
Table 1. Optimization of conditions for homocoupling of 1-bromo-4-*tert*-butylbenzene[a]



Entry	Pd	Ligand	Base	Solvent	Yield /%[b]
1	$Pd_2(dba)_3$	**1**	NaO^tBu	Diglyme	72
2	$Pd_2(dba)_3$	**2**	NaO^tBu	Diglyme	47
3	$Pd_2(dba)_3$	**3**	NaO^tBu	Diglyme	40
4	$Pd_2(dba)_3$	$P(OEt)_3$	NaO^tBu	Diglyme	37
5	$Pd_2(dba)_3$	PPh_3	NaO^tBu	Diglyme	35
6	$Pd_2(dba)_3$	—	NaO^tBu	Diglyme	NR[c]
7	$Pd(OAc)_2$	**1**	NaO^tBu	Diglyme	63
8	$Pd(CH_3CN)_2Cl_2$	**1**	NaO^tBu	Diglyme	65
9	[PdCl(allyl)]$_2$	**1**	NaO^tBu	Diglyme	57
10	$Pd(acac)_2$	**1**	NaO^tBu	Diglyme	50
11	$Pd_2(dba)_3$	**1**	NaOMe	Diglyme	33
12	$Pd_2(dba)_3$	**1**	NaOH	Diglyme	5
13	$Pd_2(dba)_3$	**1**	KO^tBu	Diglyme	ND[d]
14	$Pd_2(dba)_3$	**1**	KOMe	Diglyme	ND[d]
15	$Pd_2(dba)_3$	**1**	NaHMDS	Diglyme	5
16	$Pd_2(dba)_3$	**1**	*n*-BuLi	Diglyme	9
17	$Pd_2(dba)_3$	**1**	Cs_2CO_3	Diglyme	NR[c]
18	$Pd_2(dba)_3$	**1**	K_2CO_3	Diglyme	NR[c]
19	$Pd_2(dba)_3$	**1**	K_3PO_4	Diglyme	NR[c]
20	$Pd_2(dba)_3$	**1**	NaO^tBu	DMF	17
21	$Pd_2(dba)_3$	**1**	NaO^tBu	NMP	11
22	$Pd_2(dba)_3$	**1**	NaO^tBu	*p*-Xylene	5

[a]Reaction conditions: 1-bromo-4-*tert*-butylbenzene (1.0 mmol), solvent (3.0 mL), 5 mol % palladium, 10 mol % ligand, base (2.0 mmol), 12 h, 130 °C. [b]Yield was determined by GC by comparison to an internal standard (naphthalene). [c]No Reaction: only starting materials appeared in GC. [d]The desired homocoupling product was not detected in GC.

Table 2. Homocoupling reaction of different aryl halides[a]

Entry	ArX	Yield /%[b]	Entry	ArX	Yield /%[b]
1		80	9		45
2		61	10		62
3		65	11		60
4		75	12		48
5		75	13		30
6		72	14		33
7		21	15		27
8		10	16		14

[a]Reaction conditions: aryl halide (3.0 mmol), 2.5 mol % $Pd_2(dba)_3$, 10 mol % phosphite **1**, NaO*t*-Bu (6.0 mmol), diglyme (0.3 M), 130 °C, 12 h. [b]Isolated yields of compounds are the average of at least two runs. All compounds were characterized by comparison of ^1H and ^{13}C NMR spectra with authentic samples or literature data.

showed a better result than palladium(II) source. As for the base, sodium *t*-butoxide proved to be highly effective. In the presence of other kinds of base, the reaction yield was insufficient or zero. NaOMe and NaOH afforded very low yields of 33 and 5%, respectively (Entries 11 and 12). Using potassium bases such as KOMe and KO*t*-Bu, the desired product was not detected in GC data (Entries 13 and 14). When inorganic weak bases such as Cs_2CO_3, K_2CO_3, and K_3PO_4 were used, no reactions were observed (Entries 17, 18, and 19). The screening of several solvents indicated that the reaction in diglyme afforded a homocoupling product in good yield. Amide-type solvents such as DMF and NMP showed less than 20% yield (Entries 20 and 21). *p*-Xylene, which was a suitable solvent for the palladium/phosphite system in the Hiyama coupling,[11] afforded only trace amounts of the desired product (Entry 22).

To demonstrate the scope of this palladium–phosphite catalytic system, a variety of representative aryl halides were examined (Table 2).

As could be expected in the homocoupling of aryl halides, iodides afforded better results than the corresponding bromides or chlorides: 4-Iodotoluene afforded 80% yield, 4-bromotoluene 75% yield and 4-chlorotoluene only 14% yield (Entries 1, 5, and 16, respectively). The homocoupling product yield decreased with increasing steric hindrance of the substrate. 2-Iodotoluene showed 61% yield. Similar trends have been reported by Li et al.[14] and Wu et al.[15] However, in the present study ortho-disubstituted aryl bromides such as 2-bromobiphenyl and mesityl bromide afforded a very low yield of homocoupling product (Entries 7 and 8). Bromoanisole derivatives afforded the desired coupling products in moderate yields (Entries 9–11). Heteroaryl bromides afforded a low yield of the homocoupling products (Entries 12–14). We attempted to expand this reaction method to apply to aryl chlorides, which are more challengeable substrates. However, this catalytic system afforded less than 30% yield of the desired product.

The ^{31}P NMR spectrum of the complexation of $Pd_2(dba)_3$ and ligand **1** showed only one peak.[16] However, it showed several peaks at 0 °C.[17] In case of phosphite **2** and **3**, they showed several peaks.[16] Even though their exact coordination manners are not identified, their different manners might give the different reactivities. Further studies of coordination manners are in progress in our laboratory.

In summary, we presented the first homocoupling of aryl halides using the palladium/phosphite catalytic system. Different aryl halides were reacted in the presence of $Pd_2(dba)_3$, phosphite **1** to give symmetric biaryl compounds.

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16 The palladium complexes of phosphites (Pd/L mol ratio = 1/2) were check by ^{31}P NMR at 25 °C. Complex of **1**: δ −9.44, (141.5, 136.2, −9.44, −10.37 at 0 °C); Complex of **2**: δ 138.1 (br), 132.7 (br), 130.1(br), −12.26; Complex of **3**: δ 120.43, 85.42, −18.42.

17 Supporting Information is available electronically on the CSJ-Journal Web site; http://www.csj.jp/journals/chem-lett/.

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