



Note

Palladium catalyzed-dehalogenation of aryl chlorides and bromides using phosphite ligands

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ARTICLE INFO

Article history:

Received 16 September 2008

Received in revised form 25 October 2008

Accepted 31 October 2008

Available online 6 November 2008

Keywords:

Palladium

Phosphite

Dehalogenation

Aryl bromides

Aryl chlorides

ABSTRACT

The catalytic system based on Pd–phosphite for the dehalogenation reactions of aryl chlorides and bromides is described. The Pd–phosphite catalyst effectively promoted the dehalogenation of aryl halides to give dehalogenated products in moderate to excellent yields. The aryl chlorides required strong bases such as NaO^tBu for this transformation, whereas the aryl bromides were dehalogenated in the presence of weak bases such as Cs₂CO₃. This catalytic system exhibited tolerance to functional groups such as methoxy, amine, hydroxyl, ether, amide, benzyl and ketone groups. It also demonstrated chemoselectivity in that bromochlorobenzene was converted only to chlorobenzene.

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1. Introduction

Palladium catalyzed-transformation reactions have been widely used in organic synthesis [1]. Among them, carbon–carbon bond formation, one of the most powerful transformations, has been extensively investigated over the past 30 years [2]. Recent developments in cross-coupling methodology allow aryl halides showing high catalytic activities to be formed under milder conditions. Most of them have been affected by the ligands. Generally, electron-rich and bulky monoalkyl phosphines such as P^tBu₃ [3–5] and biphenyl alkyl phosphines [6–8] showed high activities as the ligand in the cross-coupling reaction. Moreover, a number of important developments with phosphine-free ligands such as N-heterocyclic carbenes have been reported [9]. However, they suffer some drawbacks such as sensitivity to air or moisture in the case of phosphine ligands and the requirement for multistep synthesis in the case of carbene. To address this problem, we employed a phosphite-containing, sterically hindered group as the ligand, because phosphites are less expensive and more stable to air and moisture than phosphines. They show good reactivities in Hiyama coupling reaction and the homocoupling of aryl halides [10,11]. In the latter case, we found that the dechlorination product was obtained as a byproduct when aryl chlorides were used in the homocoupling.

Organohalogenes are classified as pollutants due to their persistent toxic effect [12]. Therefore, it is important to develop efficient methods that transform them into less harmful chemicals such as

dehalogenated compounds. Numerous new dehalogenation methods using palladium [13–15], rhodium [16], iron [17] and nickel [18,19] catalysts have been reported. Palladium is the most commonly used transition metal in this transformation.

Recently, N-heterocyclic carbene ligands have been used for the dehalogenation of aryl chlorides [20], while the triphenyl phosphine ligand, which was most often used as a ligand in the palladium catalyzed-transformation, has been employed for the dehalogenation of aryl halides and alpha-haloketones [21]. However, phosphite compounds have never before been used as ligands in dehalogenation. Therefore, we decided to optimize the condition for the dehalogenation of aryl halides using the palladium/phosphites catalytic system (Fig. 1).

We employed isopropanol, possessing a beta-hydrogen, as the hydrogen source in a safer and simpler method than using molecular hydrogen. Reactions of 4-chlorotoluene with palladium in isopropanol were initially conducted using various kinds of palladium source and ligand, including phosphites. Table 1 summarizes our preliminary results for these dechlorination reactions. As expected, the ligand-free condition afforded dehalogenated product in low yield (entry 1) and Pd₂(dba)₃ was the best palladium source among the tested palladiums (entries 2–5). The phosphites showed better reactivities than the phosphines did. Phosphite **1** was the best ligand, giving the desired product in almost quantitative yield without byproduct derived from homocoupling reaction (entry 5). Phosphites **2** and **3** afforded the dehalogenated product in good yield, but gave a homocoupled compound (entries 6 and 7). However, P(OPh)₃ showed good reactivity without the formation of homocoupled product (entry 8). Interestingly, the chelating phos-

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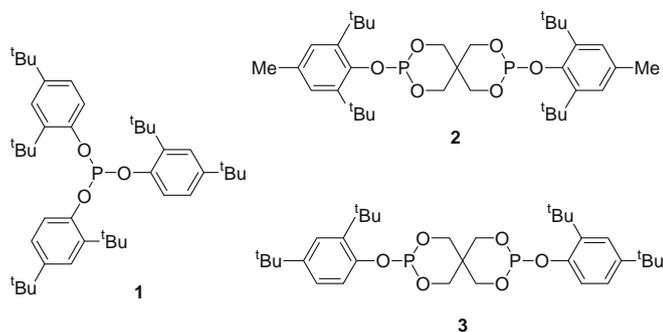


Fig. 1. Phosphite ligands.

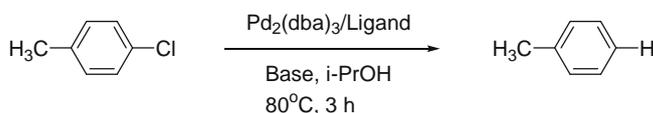
phine ligand 1,1'-bis(diphenylphosphino)ferrocene (dppf) afforded the dehalogenated product in very low yield (entry 11). Recently, Muzart and coworkers showed that dppf was a suitable ligand for dehalogenation using dimethylformamide as the hydride source. However, in this reaction system, the low reactivity of the chelating ligand is caused by blocking of the beta hydride elimination step. Sterically demanding monophosphine showed low activity (entry 12) and $\text{IPr}\cdot\text{HCl}$, which was reported by Nolan group, afforded the dehalogenated product in high yield (entry 13). When the amount of catalyst used was decreased to 1 mol%, the product yield was very low (entry 15), and a minimum catalytic loading of 2.5 mol% was needed for full conversion (entry 14). The reactivity of the dechlorination was dependent on the nature of the base. The most effective base was NaO^tBu , whereas other alkoxide bases such as KO^tBu , NaOMe and KOMe showed low product yield (entries 16–18). Therefore, the optimized conditions for the dehalogenation of aryl chlorides were as follows: 1.25 mol% $\text{Pd}_2(\text{dba})_3$, 2.5 mol% phosphite **1**, and 1.2 equiv of NaO^tBu in *i*-PrOH solvent at 80 °C for 3 h.

Next, the above optimum catalytic system was tested on aryl bromides for debromination. The data are summarized in Table 2. When 4-bromotoluene was treated with NaO^tBu using $\text{Pd}_2(\text{dba})_3$ and phosphite **1** as the ligand in *i*-PrOH, the debrominated product, toluene, was obtained in 91% yield. However, the homocoupling byproduct was also obtained in 4% yield (entry 1). To reduce the amount of byproduct, several kinds of alcohol were screened as solvents. Cyclohexanol afforded the desired product in high yield and showed a trace amount of homocoupled product (entry 4). The method using a strong base rarely addresses functional group compatibility as well as selectivity. To address these problems, we attempted to use a weak base rather than a strong base. When Cs_2CO_3 was used as a base, the conversion yield was superior to that of other weak bases such as K_2CO_3 and Na_2CO_3 (entries 5–7). When the reaction temperature was increased in the presence of Cs_2CO_3 , the toluene product was obtained in almost quantitative yield without any byproduct (entry 9). When the amount of catalytic loading was decreased to 0.5 mol%, the product yield was 99% (entry 10), whereas at 0.1 mol% catalytic loading, the yield of dehalogenated product was 60% (entry 11).

Based on the optimized condition, we investigated the scope of the dehalogenation using phosphite **1** as the ligand for a series of aryl chlorides and bromides having different electronic and steric properties. The results for aryl chlorides are summarized in Table 3. Chlorobenzene and 4-chlorotoluene were completely converted to dehalogenated product in high yields (entries 1 and 2). The *ortho*-, *meta*- and *para*-chloroanisoles all showed high yields that were independent of the substituent position (entries 3–5). This reaction method showed the tolerance to functional groups such as amino and hydroxy groups (entries 6 and 7). 1-Chloronaphthalene was converted to naphthalene in 98% yield (entry 8).

In the case of aryl bromides, the reactions were carried out with 0.5 mol% palladium and 0.5 mol% ligand at 120 °C for 10 h. Cyclohexanol and Cs_2CO_3 were employed as solvent and base, respectively. The reaction is generalized for a variety of substrates, as shown in Table 4.

Table 1
Optimization of conditions for dehalogenation of 4-chlorotoluene.^a



Entry	Palladium	Ligand	Pd mol% (Pd/L = 1/1)	Base	Conv. ^b (%)	Product ^b (%)	Homo ^c (%) ^b
1	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	–	5	NaO^tBu	35	30	– ^f
2	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	1	5	NaO^tBu	67	66	– ^f
3	PdCl_2	1	5	NaO^tBu	65	60	– ^f
4	$\text{Pd}(\text{OAc})_2$	1	5	NaO^tBu	95	94	– ^f
5	$\text{Pd}_2(\text{dba})_3$	1	5	NaO^tBu	100	99	– ^f
6	$\text{Pd}_2(\text{dba})_3$	2	5	NaO^tBu	100	95	2
7	$\text{Pd}_2(\text{dba})_3$	3	5	NaO^tBu	100	76	11
8	$\text{Pd}_2(\text{dba})_3$	$\text{P}(\text{OPh})_3$	2.5	NaO^tBu	98	92	– ^f
9	$\text{Pd}_2(\text{dba})_3$	PPh_3	2.5	NaO^tBu	76	74	– ^f
10	$\text{Pd}_2(\text{dba})_3$	$\text{P}(\text{o-tol})_3$	2.5	NaO^tBu	30	24	2
11	$\text{Pd}_2(\text{dba})_3$	Dppf^{d}	2.5	NaO^tBu	25	23	– ^f
12	$\text{Pd}_2(\text{dba})_3$	P^tBu_3	2.5	NaO^tBu	45	45	– ^f
13	$\text{Pd}_2(\text{dba})_3$	$\text{IPr}\cdot\text{HCl}^{\text{e}}$	2.5	NaO^tBu	100	99	– ^f
14	$\text{Pd}_2(\text{dba})_3$	1	2.5	NaO^tBu	100	99	– ^f
15	$\text{Pd}_2(\text{dba})_3$	1	1	NaO^tBu	15	12	– ^f
16	$\text{Pd}_2(\text{dba})_3$	1	2.5	KO^tBu	45	43	– ^f
17	$\text{Pd}_2(\text{dba})_3$	1	2.5	NaOMe	30	27	– ^f
18	$\text{Pd}_2(\text{dba})_3$	1	2.5	KOMe	5	4	– ^f

^a Reaction conditions: 1.0 mmol $\text{CH}_3\text{C}_6\text{H}_4\text{Cl}$, 3 mmol solvent.

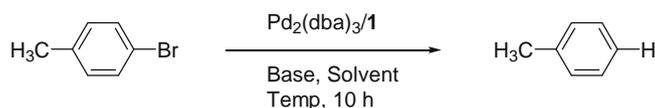
^b Yields were determined by gas chromatography (GC) by comparison to an internal standard (naphthalene).

^c Homocoupled product is 4,4'-dimethylbiphenyl.

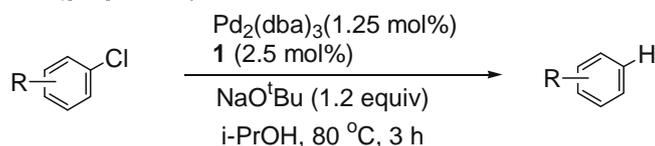
^d 1,1'-Bis(diphenylphosphino)ferrocene.

^e 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride.

^f No homocoupled product was found.

Table 2
Optimization of conditions for dehalogenation of 4-bromotoluene.^a

Entry	Pd (mol%)	Temp (°C)	Base	Solvent	Conv. (%)	Product ^b (%)	Homo ^c (%)
1	2.5	80	NaO ^t Bu	<i>i</i> -PrOH	100	91	4
2	2.5	80	NaO ^t Bu	MeOH	82	63	11
3	2.5	80	NaO ^t Bu	EtOH	94	90	2
4	2.5	80	NaO ^t Bu	Cyclohexanol	100	97	– ^d
5	2.5	80	Cs ₂ CO ₃	Cyclohexanol	60	52	3
6	2.5	80	K ₂ CO ₃	Cyclohexanol	43	35	1
7	2.5	80	Na ₂ CO ₃	Cyclohexanol	13	9	– ^d
8	2.5	100	Cs ₂ CO ₃	Cyclohexanol	80	72	2
9	2.5	120	Cs ₂ CO ₃	Cyclohexanol	100	99	– ^d
10	0.5	120	Cs ₂ CO ₃	Cyclohexanol	100	99	– ^d
11	0.1	120	Cs ₂ CO ₃	Cyclohexanol	62	60	– ^d

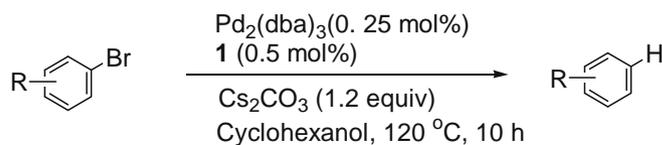
^a Reaction conditions: 1.0 mmol CH₃C₆H₄Br, 3 mmol solvent.^b Yields were determined by gas chromatography (GC) by comparison to an internal standard (naphthalene).^c Homocoupled product is 4,4'-dimethylbiphenyl.^d No homocoupled product was found.**Table 3**
The dehalogenation of aryl chlorides using palladium/phosphite catalyst.

Entry	Aryl chloride	Conv. (%)	Yield ^a (%)	Entry	Aryl chloride	Conv. (%)	Yield ^a (%)
1		100	>99 ^b	5		100	>99 ^b
2		100	98	6		100	96
3		100	>99 ^b	7		100	95
4		100	>99 ^b	8		100	98

^a All compounds are characterized by comparison of gas chromatography (GC) analysis, ¹H and ¹³C NMR spectra with authentic samples or literature data.^b Almost quantitative yield.

Bromobenzene, 4-bromotoluene and 1-bromo-4-*tert*-butylbenzene were converted to the corresponding debrominated products in high yields (entries 1–3, respectively). 3-Bromoanisole showed moderate yield even though the conversion was high, and the homocoupled product was not found in gas chromatography (GC) (entry 4). However, 4-bromoanisole afforded 4,4'-dimethoxybiphenyl as byproduct in 5% yield (entry 5). Even sterically demanding substrates were converted to the desired product in high yields (entries 6 and 7). In a similar method to that of aryl chloride, this reaction method provided the tolerance to functional group such as amino, nitro, hydroxyl and ether (entries 8–11). 2-Bromo-6-methoxynaphthalene was transformed to 2-methoxynaphthalene in 95% yield (entry 12). 4-Bromobiphenyl

was converted to the biphenyl in 99% yield (entry 13). 2-Bromobiphenyl, which is more sterically hindered, showed low conversion and low yield. Nevertheless, its yield was increased to 99% when NaO^tBu was used as the base instead of Cs₂CO₃ (entry 14). In the case of 2-bromothiophene, the yields of conversion and product were low when Cs₂CO₃ was used as the base. However, when NaO^tBu was used as the base, 2-bromothiophene was completely converted to thiophene in 72% yield and produced bithiophene as the byproduct in 10% yield (entry 15). The reactivity of 3-bromopyridine was higher than that of 2-bromopyridine. 2-Bromopyridine and 3-bromopyridine resulted in homocoupled products as byproduct in 7% and 15% yield, respectively (entries 16 and 17). This reaction condition exhibited chemoselectivity

Table 4The dehalogenation of aryl bromides using palladium/phosphite catalyst.^a

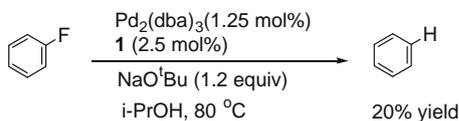
Entry	Aryl bromide	Conv. (%)	Yield (%)	Entry	Aryl bromide	Conv. (%)	Yield (%)
1		100	98	12		100	95
2		100	95	13		100	99
3		100	99	14		50 (100) ^d	46(99) ^d
4		98	78 ^b	15		40 (100) ^d	38(72) ^{d,e}
5		98	78 ^c	16		63	43 ^f
6		90	84	17		98	65 ^g
7		87	85	18		99	88
8		84	80	19		99	89
9		100	85	20		100	98
10		100	61 ^b	21		100	99
11		90	85	22		100	66 ^b

^a All compounds are characterized by comparison of gas chromatography analysis, ¹H and ¹³C NMR spectra with authentic samples or literature data.^b No homocoupled product was found in gas chromatography (GC).^c 5% Homocoupled byproduct.^d NaO^tBu was used as base instead of Cs₂CO₃.^e 10% Homocoupled byproduct.^f 7% Homocoupled product.^g 15% Homocoupled product.

to aryl bromide. 3- and 4-Chlorobromobenzenes were converted to chlorobenzene. Bromotoluene and benzene were not found in the reaction mixture, confirming that only debromination occurred (entries 18 and 19). Yus' group did not achieve the halogen chemoselectivity using copper catalyst [22]. The substrates hav-

ing amide and ketone groups also afforded the corresponding debrominated products in moderate to excellent yields without reducing the carbonyl group (entries 20–22).

As shown in Scheme 1, when the dehalogenation of fluorobenzene was carried out under reaction condition that was used for



Scheme 1. Palladium-catalyzed defluorination.

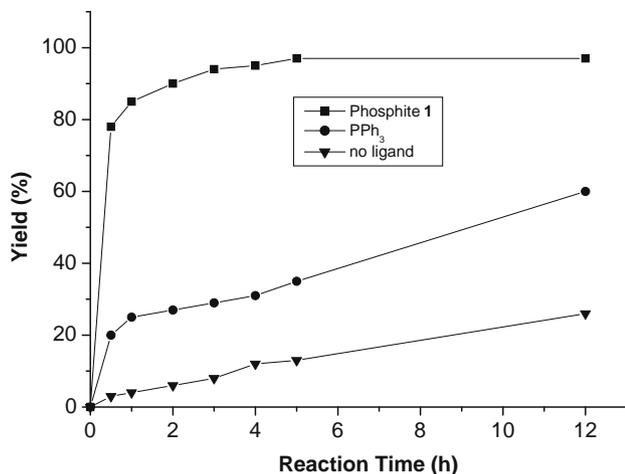
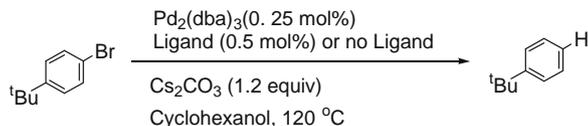


Fig. 2. Reaction rate of debromination with phosphite **1** and PPh₃.

dechlorination, the yield of defluorinated product, benzene, was only 20% as determined by GC. This low yield was attributed to the strong bond formed between carbon and fluorine atoms.

We compared the reaction rates of the phosphite ligand **1** and PPh₃ in the debromination of 1-bromo-4-*tert*-butylbenzene. As shown in Fig. 2, phosphite **1** showed better catalytic activity than PPh₃. In addition, the debromination without ligand showed very low reactivity.

The general mechanism of the palladium-catalyzed dehalogenation is described in Fig. 3 [23]. The palladium(0) is the catalytically active species that generates the oxidative adduct complex. Metal alkoxide, which is generated from the reaction with alcohol and base, attacks the palladium and displaces the halogen atom. The palladium-hydride complex that is produced through the beta hydride elimination affords a reduced arene product and regenerates the palladium(0) catalyst. The fact that the cyclohexanone was obtained with the same amount of debrominated products in all case of Table 4 supported the proposed mechanism.

The phosphorus atom of phosphite **1** is more electron-poor than that of triphenylphosphine. However, the former had better reactivity than the latter, as shown in Fig. 2, which is contrary to the general belief that electron-rich ligands accelerate the rate of oxidative addition of aryl halides [24]. It is generally believed that the rate determining step for dehalogenation is the oxidative addition of aryl halides. However, in this case, we believe that the phosphite ligand exerted much greater effect on both the beta hydride elimination and the reductive elimination steps. The π acceptor phosphite ligand accelerated the beta hydride elimination step while the sterically bulky substituted group in phos-

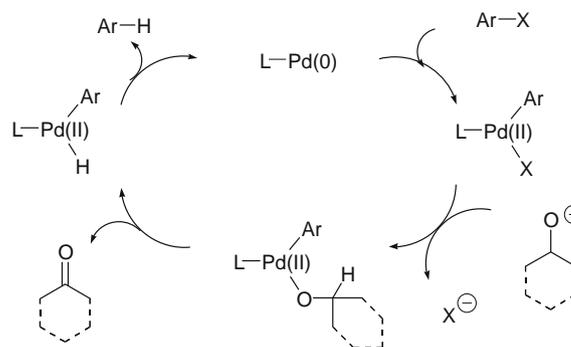


Fig. 3. General mechanism of Pd-catalyzed dehalogenation.

phites accelerated the reductive elimination steps. Further mechanistic studies of the reactivity of phosphite ligand are in progress in our laboratory.

In conclusion, we demonstrated that the sterically hindered phosphites exhibited good reactivities as ligands in the dehalogenation of aryl bromides and chlorides. To the best of our knowledge, this is the first report of the use of phosphite as a ligand in dehalogenation reactions. Aryl chloride required 2.5 mol% catalyst and a strong base, while 0.5 mol% catalytic loading was sufficient for the debromination of aryl bromide in the presence of a weak base. Aryl bromides bearing functional groups such as alkyl, alkoxy, hydroxyl, ether, chloro, phenyl, amide, benzyl and ketone can be transformed to the corresponding debrominated products in high yields.

Acknowledgment

This work was supported by the Korea Research Foundation Grant Funded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2006-003-C-00178).

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