Palladium(II) Phosphine-Ylide Complexes as Highly Efficient Homogeneous Pre-catalysts for the Ullmann Homocoupling Reaction of Aryl Halides

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A highly efficient Ullmann homocoupling reaction of aryl halides using palladium(II) phosphine-ylide complexes as homogenous pre-catalysts under aerobic conditions has been developed without the need for any chemical co-reducing agents. The procedure is relatively mild and appears to have broad applicability, being useful for the homocoupling of both electron-deficient and electron-rich aryl halides and also homocoupling of phenylboronic acid and phenylacetylene.

INTRODUCTION

The Ullmann reaction has evolved considerably from its original guise as the homocoupling of aryl halides in the presence of an excess of copper powder at elevated temperatures [1]. In the last decades, there were notable improvements to the Ullmann reaction. Last decade, more and more attentions have been paid in Pd-catalyzed homocoupling reactions, which are usually conducted in the presence of the reducing agents, such as zinc [2], hydrogen gas [3], formate salts [4], hydroquinone (HQ) [5], alcohols [6], gas [7], amines [8], indium [9] and triphenylarsine [10]. Some of these reducing agents, however, reduce the selectivity in some cases due to the competitive chemisorption and hydride forming ability, which leads to the parallel reduction reaction. For example, undesired reductions of carbonyl and nitro group as well as hydro dehalogenation are often observed when metal was employed as the reductant. Recently, some compounds had been used as ligands in palladium-catalyzed homocoupling reactions of aryl halides such as P(o-tol)$_3$ and As(o-tol)$_3$ [11], P(2-furyl)$_3$ [12], N,N-dicyclohexyl-1,4-diazabutadiene (DAB-Cy) [13], tetrakis(dimethylamino)ethylene (TDAE)

[14], biphenyl-based phosphine system [15], agarose hydrogel [16], poly ethylene glycol [17], tetrabutylammonium bromide and fluoride [18], Pd@IFMC [19], EDTA [20], palladium on carbon [21], phosphite [22], carboxylate-based ionic liquids [23], N-heterocyclic carbine-Pd polymers [24], tert-butyllithium [25], polystyrene-supported triphenylarsines [26], monomeric orthopalladated complex of 4-methoxybenzoylmethylene-triphenylphosphorane [27], 1,4-butanediol [28], polymerized functional ionic liquid [29] and immobilization of Pd(II) on MOFs [30]. Here, we would like to report the simple palladium (II) phosphine-ylide complexes [31] as an effective homogeneous pre-catalysts for Ullmann homocoupling reactions of aryl halides without using any reductant.

EXPERIMENTAL

General Procedure for the Homocoupling of Aryl Halides Catalyzed by Complex A or B

NaOH (3 mmol, 0.1 g) and aryl halide (1.0 mmol) were added to the vessel containing complex A or B (0.5 mol%) and DMF (3 ml) at 130 °C under the air atmosphere and stirred for the appropriate time. TLC of the reaction mixture showed the completion of the reaction after 1-12 h. The

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reaction mixture was then cooled to room temperature. After extraction with water and ether, the combined organic layer was dried over $MgSO_4$. Evaporation of the solvent and chromatography on a short silica gel column using n-hexane/ethyl acetate (5:1) as eluent gave corresponding biaryl products in 65%-95% yields (Table 3, entries 1-12). The products were identified by comparison of their physical and spectral data with the literature [34-39].

Homocoupling Reaction of Phenylboronic Acid Catalyzed by Complex A

NaOH (0.1 g, 3 mmol) and phenylboronic acid (0.12 g, 1 mmol) were dissolved in DMF (3 ml) in a flask. To the resulting solution, complex A (0.022 g, 0.5 mol%) was added while being stirred at 90 °C under the air atmosphere for 1 h. The mixture was cooled to room temperature. After extraction with water and ether, the combined organic layer was dried over $MgSO_4$. Purification of the product was performed by column chromatography on silica gel eluted with an appropriate mixture of n-hexane/ ethyl acetate (5:1) to afford the pure biphenyl compound in 92% isolated yield.

Homocoupling Reaction of Phenylacetylene Catalyzed by Complex A

To a flask containing DMF (3 ml), complex A (0.022 g, 0.5 mol%), phenylacetylene (0.102 g, 1 mmol) and NaOH (0.1 g, 3 mmol) were added and the resulting mixture was stirred at 90 °C for 4 h under the air atmosphere. The mixture was cooled down to room temperature. After extraction with water and ether, the combined organic layer was dried over $MgSO_4$. Evaporation of the solvent and chromatography on a short silica gel column using n-hexane/ethyl acetate (5:1) as eluent gave corresponding dienyne product in 70% isolated yield.

Physical and Spectral Data of the Products

a. White crystals, m.p: 70-71 °C (lit. 69-70 °C) [32], ^{1}H NMR (250 MHz, $CDCl_3$): 7.66-7.35 (m, 10H), ^{13}C NMR (62.5 MHz, $CDCl_3$): 145.2, 131.2, 127.4, 127.1.

b. White crystals, m.p.: 177-178 °C (lit. 178-179 °C) [33], ^{1}H NMR (250 MHz, $CDCl_3$): 7.48-7.40 (m, 4H), 6.9-6.8 (m, 4H), 3.70 (s, 6H), ^{13}C NMR (62.5 MHz, $CDCl_3$): 158.6, 132.7, 127.7, 113.8, 55.55.

c. White crystals, m.p.: 119-120.5 °C (lit. 118-120 °C)

[34], ^{1}H NMR (250 MHz, $CDCl_3$): 7.43-7.34 (m, 4H), 7.22-7.10 (m, 4H), 2.55 (s, 6H), ^{13}C NMR (62.5 MHz, $CDCl_3$): 138.8, 137, 130.2, 126.8, 21.3.

d. White solid, m.p.: 188-189 °C (lit. 189-190 °C) [35], ^{1}H NMR (250 MHz, $CDCl_3$): 7.98 (d, J = 8.6 Hz, 4H), 7.68 (d, J = 8.6 Hz, 4H), 2.75 (s, 6H), ^{13}C NMR (62.5 MHz, $CDCl_3$): 195.6, 145.5, 137.8, 128.5, 125.5, 29.0.

f. Yellow solid, m.p.: 238-240 °C (lit. 240 °C) [35], ^{1}H NMR (250 MHz, $CDCl_3$): 7.85-7.80 (m, 4H), 7.47-7.44 (m, 4H), ^{13}C NMR (62.5 MHz, $CDCl_3$): 152.5, 148.2, 125.9, 124.8.

g. ^{1}H NMR (250 MHz, $CDCl_3$): 10.21 (s, 2H), 8.02 (d, J = 8.4 Hz, 4H), 7.90 (d, J = 8.4 Hz, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 191.5, 145.8, 136.6, 130.5, 126.8.

h. Orange solid, m.p.: 232-233 °C (lit. 232 °C) [36], ^{1}H NMR (250 MHz, $CDCl_3$): 8.77 (s, 2H), 8.4-8.6 (m, 6H), 7.75-7.89 (m, 4H), 7.43-7.46 (m, 5H), ^{13}C NMR (62.5 MHz, $CDCl_3$): 150.5, 148.8, 136.5, 134.5, 123.4.

i. White crystals m.p.: 85-87 °C (lit. 85-86 °C) [37], ^{1}H NMR (250 MHz, $CDCl_3$): 7.5-7.45 (m, 4H), 7.32-7.2 (m, 6H), ^{13}C NMR (62.5 MHz, $CDCl_3$): 133.6, 129.2, 128.5, 121.7, 80.7, 73.1.

RESULTS AND DISCUSSION

In continuation of the interest in the developing new catalyst for the C-C coupling reaction [38], we report here homogeneous homocoupling reactions catalyzed by two palladium(II) phosphine-ylide complexes A and B which recently developed [31]. In these title complexes, the phosphorus ylide as a ligand coordinated to the palladium atom *via* the phosphine group and ylidic carbon atom to form a six-membered chelate ring (Fig. 1). It is well established that palladium complexes containing phosphorus ylides, which combine both good donor strength and π-accepting capacity, have a high catalytic activity [39].

The rate of coupling is dependent on a variety of parameters such as solvent, base, and catalyst loading. Hence, we investigated the effects of different reaction parameters on the catalytic activity in order to optimize the protocol for a homocoupling reaction.

In the first, we investigated the effect of different solvents (Table 1, entries 1-7) on the model reaction of bromobenzene catalyzed by 0.5 mol% of catalyst A, under

X= OCH$_3$ **A**
X= Br   **B**
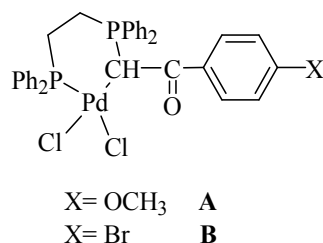
Fig. 1.

Table 1. Optimization of Base and Solvent for Homocoupling Reaction of Bromobenzene[a]
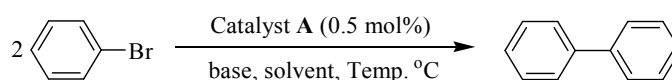
Entry	Solvent	Base	Temp. (°C)	Time (h)	Yield (%)[b]
1	Dioxane	NaOH	130	10	50
2	Toluene	NaOH	130	14	55
3	Methanol	NaOH	65	20	75
4	CH$_3$CN	NaOH	80	8	80
5	DMSO	NaOH	130	5	95
6	DMF	NaOH	130	2	98
7	DMF	None	130	24	-
8	DMF	K$_2$CO$_3$	130	5	70
9	DMF	Na$_2$CO$_3$	130	5	75
10	DMF	Cs$_2$CO$_3$	130	3	90
11	DMF	NaOAc	130	7	68
12	DMF	Et$_3$N	130	8	trace

[a]Reaction conditions: Bromobenzene (1 mmol), catalyst A (0.5 mol%), base (3 mmol), solvent (3 ml) under air. [b]Isolated yield.

air. NaOH was used as a base in this reaction. The solvent had a dramatic influence on product formation. As clear from Table 1, the yield of biphenyl was reduced as the polarity of the organic solvent decreased. Moderate product yields were observed when the reactions were performed in solvents of low polarity, such as 1,4-dioxane, and toluene (Table 1, entries 1, 2). High yields were observed when highly polar solvents, such as acetonitrile, dimethylformamide (DMF), dimethylsulfoxide (DMSO), and methanol were used as the reaction medium (Table 1,

Table 2. The Effect of the Amount of Catalyst in Homocoupling Reaction of Bromobenzene[a]

$$2 \text{ } C_6H_5-Br \xrightarrow[\text{NaOH, DMF, 130 °C}]{\text{Catalyst A or B}} C_6H_5-C_6H_5$$
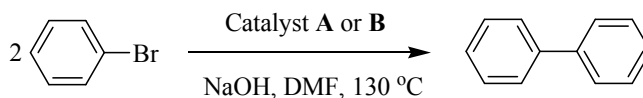
Entry	Catalyst (mol%)	Yield (%)[b]
1	None	0
2	A (1.0)	97
	B (1.0)	95
3	A (0.5)	95
	B (0.5)	95
4	A (0.1)	70
	B (0.1)	73
5	A (0.01)	50
	B (0.01)	54

[a]Reaction conditions: Bromobenzene (1 mmol), NaOH (3 mmol), DMF (3 ml), 130 °C, under air. [b]Isolated yield.

entries 3-6). As shown in Table 1, DMF gave the highest yield (entry 6, 98%) after 1.5 h at 130 °C.
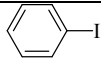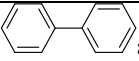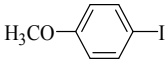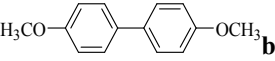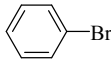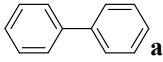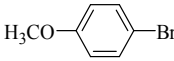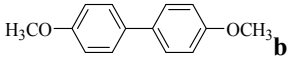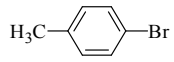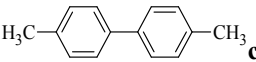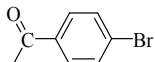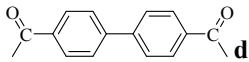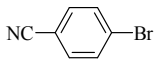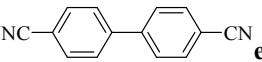
Next investigated the influence of various bases (Table 1, entries 7-11) on the model system using 0.5 mol% of catalyst A under the air atmosphere. Under identical reaction conditions, bases such as NaOH, K_2CO_3, Et_3N, Cs_2CO_3, Na_2CO_3 and NaOAc led to considerable variation in the isolated yields. However, only NaOH and Cs_2CO_3 gave acceptable results with DMF as the solvent. Based on the results shown in Table 1, NaOH was the best choice (entry 6).
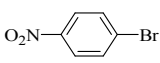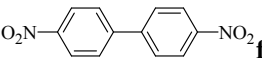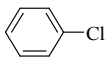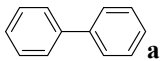
The effects of catalyst loading were also examined. The results were summarized in Table 2. A control experiment indicated that the coupling reaction did not occur in the absence of catalyst A or B (Table 2, entry 1). A catalyst loading of 0.5 mol% was found to be optimum (Table 2, entry 3).
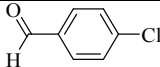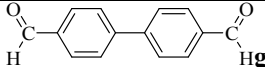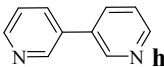
Using the optimized conditions, we examined the scope of the reaction of various aryl halides using catalyst A and B. The results are shown in Table 3. Both electron-rich and electron-poor aryl bromides could be used to provide the homocoupling products in moderate to good yields. Iodobenzene showed higher reactivity (Table 3, entry 1). The reductive homocoupling of aryl bromides substituted with electron-deficient groups was a rather difficult task and proceeded in longer reaction times (Table 3, entry 6, 8). Poor catalytic activity for chlorobenzene was observed as only a yield of 10% was obtained even with 4 mol% of A and reacting for 24 h (Table 3, entry 9) but when electron-deficient aryl chloride such as 4-bromo benzaldehyde was used, 20% of biaryl compound was obtained (Table 3, entry 10). 3-Bromopyridine was used as a heterocyclic aryl halide and its homocoupling reaction was examined. Reductive homocoupling of 3-bromopyridine proceeded smoothly and the coupling product was isolated in 65% yield (Table 3, entry 11). Similar results were also obtained in the presence of catalyst B (Table 3) but the reaction times were longer than the reaction times of catalyst A.

Table 3. Homocoupling Reactions of Various Aryl Halides Catalyzed by Catalyst A or B[a]
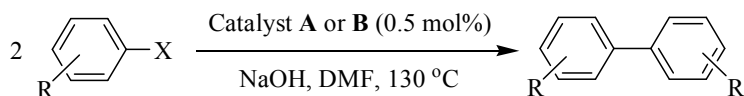
Entry	Ar-X	Product[b]	Time (h)	Catalyst	Yield (%)[c]	TON[e]	TOF (h^{-1})[f]
1		a	1	A	95	1.90	1.90
			2.5	B	95	1.90	0.76
2		b	6	A	88	1.76	0.29
			7.5	B	90	1.80	0.24
3		a	2	A	93	1.86	0.93
			4	B	90	1.80	0.45
4		b	6.5	A	85	1.70	0.26
			8	B	90	1.80	0.23
5		c	6.5	A	83	1.66	0.26
			8	B	80	1.60	0.20
6		d	12	A	78	1.56	0.13
			15	B	75	1.50	0.10
7		e	24	A	-	-	-
			24	B	-	-	-
8		f	12	A	70	1.40	0.12
			14	B	68	1.36	0.10
9		a	24	A	15[d]	0.04	0.001
			24	B	10[d]	0.03	0.001

Table 3. Continued

10			24	A	20	0.40	0.02
			24	B	15	0.30	0.01
11			12	A	65	1.3	0.11
			15	B	67	1.34	0.90

[a]Reaction conditions: Aryl halide (1 mmol), catalyst A or B (0.5 mol%), NaOH (3 mmol), DMF (3 ml), 130 °C, under air. [b]All products are known compounds and were identified by comparison of their physical or spectral data with those of known samples [32-37]. [c]Isolated yield. [d]4 mol% of A or B was used. [e]TON, turnover number, moles of aryl halides converted per mole of Pd. [f]TOF, turnover frequencies, TON/time of reaction.
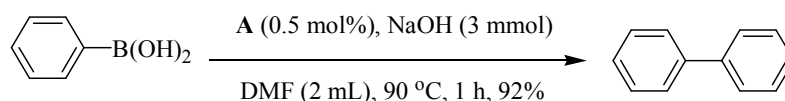
Scheme 1
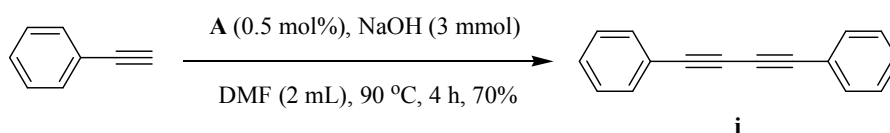
Scheme 2

In order to show the more application of this catalytic system, the homocoupling reaction of phenylboronic acid and phenylacetylene under similar reaction conditions have been also presented. The reactions were performed well as shown in Schemes 1 and 2 and the desired coupled products were isolated in 92% and 70%, respectively.

Electrochemistry is a convenient technique to detect Pd(0) complexes that are generated in situ from Pd(II) complexes. The electrochemical behavior of complexes was investigated by cyclic voltammeters [31], thus cyclic voltammetry (CV) of complexes A and B, in dichloromethane solution with Pt electrode, shows that the redox reaction of the pair Pd(II)/Pd(0) is irreversible with the cathodic peak potential at -1.08 V versus Ag wire. There is no anodic peak(s) observed on the reverse scan. This behavior is similar to that reported previously in a cyclic

voltammetric study of various types of Pd(II) complexes in aprotic solvents [40]. This irreversibility may be due to the reaction of a Pd(0) complex with adventitious O_2 or other components of the solution [41]. Therefore, we conclude that the reaction mechanism occurs *via* the reduction of Pd(II) to Pd(0) in the homocoupling cycle.

CONCLUSIONS

In summary, we have shown the applicability of the palladium(II) phosphine-ylide complexes A and B as efficient and well-defined homogenous pre-catalysts for Ullmann homocoupling reaction of various aryl halides without the need for any chemical co-reducing agents. High activity and air stability of the catalyst, the high solubility of catalyst in organic solvents, low catalyst loadings, high

yields of corresponding homocoupling product, and short reaction times are important features of using this homogeneous system. In addition to the homocoupling reactions of aryl halides, important high yielding homocoupling reactions of phenylboronic acid and phenylacetylene using this catalytic system have been conducted in the presence of these catalysts.

ACKNOWLEDGEMENTS

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