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Synthesis of a new palladium salt using *N*-benzyl DABCO chloride and its application in Suzuki reaction

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A palladium catalyst was synthesized using *N*-benzyl DABCO chloride and palladium chloride. The structure of this catalyst was characterized and then the catalyst was used in Suzuki cross- coupling reaction of different aryl halides with arylboronic acids. All substrates afforded the corresponding products in good to high yields in the presence of low amounts of the catalyst. Under the heating conditions employed, cheaper and more available aryl chlorides gave relatively high yields in the Suzuki reaction. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: N-benzyl DABCO chloride; palladium chloride; Suzuki coupling; aryl halide; arylboronic acid

Introduction

The cross-coupling of aryl halides with arylboronic acids, namely the Suzuki-Miyaura coupling reaction, has become one of the most powerful, versatile and popular tools for the selective construction of carbon-carbon bonds.^[1-4] The obtained biaryls are important structural moieties in numerous polymers, agrochemicals, natural products and pharmaceutical intermediates,[5-10] making the Suzuki reaction an important and common tool in organic synthesis. Over the past two decades, efforts have been made to develop efficient catalytic systems for the Suzuki-Miyaura coupling reaction. In this regard, palladium-phosphine complexes are among the most commonly employed catalysts of choice.^[11–18] However, some of the phosphorous ligands are sensitive to air and moisture and economically and environmentally undesirable due to difficulties with their recovery and the formation of toxic phosphines as byproducts in the reaction.^[19] Therefore, designing efficient and phosphine-free ligands is still an important issue.^[20]

Although simple amines are generally used in cross-coupling reactions as bases and display some properties as ligands to stabilize the reactive palladium intermediates,^[21,22] only a few papers have reported the use of simple amines as ligands combined with Pd(0) to efficiently catalyze the Suzuki-Miyaura cross-coupling reaction.^[23,24] However, in comparison to primary and secondary amines, employing the tertiary amines as ligands showed no activity or low activity for the reaction. In 2004, for the first time Li et al. reported that Pd(OAc)2/DABCO as a tertiary amine is a stable, inexpensive and highly efficient catalyst system for the Suzuki-Miyaura reaction of aryl halides and arylboronic acids.^[25] They subsequently examined the effect of different solvents on the reaction rate and catalyst reusability.^[26,27] However, there is no report concerning the use of DABCO salts in the Suzuki reaction. In this study, initially a palladium catalyst was synthesized using 1-benzyl-4-aza-1-azaniabicyclo [2.2.2]octane chloride (N-benzyl DABCO chloride) and palladium chloride, and this catalyst was then used in the Suzuki reaction of aryl iodides, aryl bromides and aryl chlorides with arylboronic acids.

Results and Discussion

The palladium catalyst was synthesized by the reaction of *N*-benzyl DABCO chloride and palladium chloride in acetone as the solvent. The resulting solids were easily separated and washed with water to remove the unreacted *N*-benzyl DABCO chloride. The structure of the produced catalyst was characterized using ¹H NMR, ¹³C NMR, IR and elemental analysis. In 1999, Bouquillon *et al.* reported that the addition of quaternary ammonium salt (tetrabutyl ammonium chloride) to PdCl₂ led to formation of stable dinuclear complex.^[28] Based on their investigations and elemental analysis of our catalyst, the structure of synthesized catalyst was suggested as shown in Scheme 1.

To evaluate the catalytic activity, it was applied in the Suzuki cross-coupling reactions of aryl halides and arylboronic acids. To optimize the reaction conditions, the effects of the solvent, base, temperature and the amount of catalyst on the cross-coupling reaction were first investigated using a model reaction of 4-bromobenzonitrile and 9-bromophenanthrene as a bulky aryl bromide with phenylboronic acid. Initially, the reaction was investigated in the presence of 1 equiv. of K_2CO_3 as the base and 0.35 mol% of catalyst in different solvents and at various temperatures. It seems that water can be a suitable and green solvent for this reaction; however, repeating the reaction for 4-bromobenzonitrile at 60°C and 9-bromophenanthrene at 100°C proved that water is not an appropriate solvent. Among the various solvents, methanol seems to be the best one and gave the highest yield in a shorter reaction time (Table 1). Since ethanol is

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Scheme 1. Synthesis of catalyst A from N-benzyl DABCO chloride and palladium chloride.

Table 1. Optimization of reaction conditions catalyzed by catalyst A ^a								
		ArBr	+ - B(OH)2	catalyst A solvent, base	► ► Ar			
Entry	Ar	Solvent	Temperature (°C)	Base	Catalyst (mol%)	Time (min)	Conversion (%) ^b	
1	4-CN&bondC ₆ H ₄	DMF	140	K ₂ CO ₃	0.35	140	100	
2	4-CN&bondC ₆ H ₄	DMF	100	K ₂ CO ₃	0.35	190	100	
3	4-CN&bondC ₆ H ₄	NMP	120	K ₂ CO ₃	0.35	200	100	
4	4-CN&bondC ₆ H ₄	CH₃CN	80	K ₂ CO ₃	0.35	120	92	
5	4-CN&bondC ₆ H ₄	H ₂ O	100	K ₂ CO ₃	0.35	30	100	
6	4-CN&bondC ₆ H ₄	H ₂ O	60	K ₂ CO ₃	0.35	60	0	
7	9-Phenanthrene	H ₂ O	100	K ₂ CO ₃	0.35	105	0	
8	4-CN&bondC ₆ H ₄	Dioxane	90	K ₂ CO ₃	0.35	130	67	
9	4-CN&bondC ₆ H ₄	Methanol	50	K ₂ CO ₃	0.35	20	100	
10	9-Phenanthrene	Methanol	50	K ₂ CO ₃	0.35	30	80	
11	4-CN&bondC ₆ H ₄	Ethanol	60	K ₂ CO ₃	0.35	20	100	
12	4-CN&bondC ₆ H ₄	Ethanol	60	Na ₂ CO ₃	0.35	95	100	
13	4-CN C ₆ H ₄	Ethanol	60	NaOAC	0.35	60	100	
14	4-CN&bondC ₆ H ₄	Ethanol	60	Cs ₂ CO ₃	0.35	15	100	
15	9-Phenanthrene	Ethanol	60	Cs ₂ CO ₃	0.35	20	95	
16 ^c	4-CN&bondC ₆ H ₄	Ethanol	60	K ₂ CO ₃	0.35	5	100	
17 ^c	4-CN&bondC ₆ H ₄	Ethanol	60	K ₂ CO ₃	0.2	5	100	
18 ^c	4-CN&bondC ₆ H ₄	Ethanol	60	K ₂ CO ₃	0.1	5	100	
19 ^c	4-CN&bondC ₆ H ₄	Ethanol	60	K ₂ CO ₃	0.05	5	100	
20 ^c	4-CN&bondC ₆ H ₄	Ethanol	r.t.	K ₂ CO ₃	0.05	10	100	
21 ^c	9-Phenanthrene	Ethanol	r.t	K ₂ CO ₃	0.05	20	50	
^a Reaction	^a Reaction conditions: ArBr (1 mmol), phenylboronic acid (1.2 mmol), base (1 equiv.), 1solvent (2 ml), catalyst A .							

^bDetermined by GC.

^cBase (2 equiv.).

greener and the results are almost the same, ethanol was chosen as the best solvent. The effects of different bases on this reaction were examined and the results showed that Cs_2CO_3 is the best. However, as K₂CO₃ is less expensive and is readily available and the results are similar, K₂CO₃ was selected as the optimum base. Increasing the amount of K₂CO₃ to 2 equiv., the reaction time decreased from 20 to 5 min. Therefore, 2 equiv. of this base were used in the subsequent reactions. Finally, the effect of different amounts of the catalyst was investigated and, as can be seen in Table 1, various amounts of catalyst did not influence the reaction time and conversion; therefore the reaction was repeated with 0.05 mol% of catalyst at room temperature. In order to ensure that the reaction proceeds at room temperature, the reaction of 9-bromophenanthrene was carried out under the stated conditions and the conversion of 50% in 20 min was a good reason to select room temperature as the best condition.

As the application of aryl chlorides in the Suzuki reaction has attracted much attention in recent years, because they are less expensive and readily available, we also tried to improve the reaction conditions in order to make them applicable to less reactive aryl chlorides. To do this, the reaction of 1-chloro-4-nitrobenzene and phenylboronic acid in the presence of 2 equiv. of K_2CO_3 and 0.05 mol% catalyst was chosen and the effects of different solvents, temperatures and tetrabutylammonium bromide (TBAB) as an ionic liquid were also tried. As demonstrated in Table 2, adding 0.1 mmol TBAB caused a dramatic increase in the rate and yield of the reaction. The best result was obtained when the reaction was carried out in DMF as the solvent and at 100°C in the presence of 0.1 mmol TBAB. To ensure that the reaction of aryl chlorides proceeded completely, all reactions were allowed to stay at optimum conditions for 10 h and then the products were isolated.

With optimal conditions in hand, we carried out the reaction of various aryl halides with phenylboronic acid (Table 3). Bulky aryl halides such as 1-bromonaphthalene and 9-bromophenanthrene reacted much more slowly with phenylboronic acid and their

Table 2. Optimization of reaction conditions for aryl chlorides ^a								
	O ₂ N-CI	+	catalyst A solvent, K ₂ CO ₃	0 ₂ N-				
Entry	Solvent (v/v)	Temperature (°C)	Additives	Time (h)	Conversions (%) ^b			
1	Ethanol	r.t	_	7	5			
2	Ethanol	60	_	5	5			
3	PEG(400)	110	_	10	30			
4	PEG(400)/H ₂ O (2:1)	110	_	10	30			
5	DMF	110	_	10	40			
6	DMF	100	TBAB	1	60			
7	DMF/H ₂ O (2:1)	100	TBAB	5	50			
^a Reaction conditions: 1-chloro-4-nitrobenzene (1 mmol), phenylboronic acid (1.2 mmol), K ₂ CO ₃ (2 equiv.), catalyst A (0.05 mol%), solvent (2 ml). ^b Determined by GC.								

Table 3. Coupling reactions of aryl halides with anylboronic acids under the optimized conditions ^a									
R_1 X $+$ R_2 $B(OH)_2$ $Catalyst A$ R_1 R_2 R_2									
Entry	Х	R ¹	R ²	Temperature (°C)	Time (h)	Yield (%) ^b [ref.]			
1	Br	Н	Н	r.t	0.25	99 ^[29]			
2	I	Н	Н	r.t	0.33	99 ^[29]			
3	I	4-OMe	Н	r.t	1.25	89 ^[29]			
4	I	4-OMe	Н	60	0.25	87 ^[29]			
5	Br	4-OMe	Н	r.t	0.7	98 ^[29]			
6	Br	4-COCH ₃	Н	r.t	0.42	93 ^[29]			
7	Br	4-CHO	Н	r.t	0.25	96 ^[30]			
8	Br	4-CN	Н	r.t	0.2	98 ^[30]			
9	Br	1-Naphthalene	Н	r.t	1.25	80 ^[31]			
10	Br	1-Naphthalene	Н	60	0.5	85 ^[31]			
11	Br	9-Phenanthrene	Н	r.t	0.7	50 ^[32]			
12	Br	9-Phenanthrene	Н	60	1	85 ^[32]			
13	Br	4-NO ₂	Н	r.t	3	90 ^[29]			
14	Br	4-NO ₂	Н	60	0.25	97 ^[29]			
15	Br	2-NO ₂	Н	r.t	24	50 ^[35]			
16	I	4-NO ₂	Н	r.t	2	95 ^[29]			
17	Br	4-Cl	Н	r.t	0.5 min	86 ^[29]			
18	Br	3-Cl	Н	r.t	1 min	97 ^[36]			
19	Br	2-Cl	Н	r.t	2 min	98 ^[33]			
20	Br	4-Cl	OMe	r.t	3 min	91 ^[29]			
21	Br	4-COCH ₃	OMe	r.t	1.25	80 ^[34]			
22	Br	4-CHO	OMe	r.t	0.5	90 ^[34]			
23	Br	4-CN	OMe	r.t	0.6	90 ^[34]			
24 ^c	CI	Н	Н	100	10	85 ^[29]			
25 ^c	CI	4-CHO	Н	100	10	88 ^[30]			
26 ^c	CI	4-COCH ₃	Н	100	10	87 ^[29]			
27 ^c	Cl	4-NO ₂	Н	100	10	98 ^[29]			
28	Cl	4-NO ₂	Н	r.t	7	5 ^[29]			

^aReaction conditions: aryl halide (1 mmol), arylboronic acid (1.2 mmol), K₂CO₃ (2 equiv.), catalyst **A** (0.05 mol%), ethanol (2 ml) at room temperature. ^bIsolated yields.

^cThe reactions were carried out in the presence of TBAB (0.1 mmol) and in DMF as the solvent for 10 h.

Table 4. the comparison of TON and TOF for catalyst A and other DABCO based catalytic systems

Aryl halide				Catalytic	: system			
	Pd(OAC) ₂ /DABCO/ acetone		Pd(OAC) ₂ /DABCO/ PEG-400		Pd(OAC) ₂ /DABCO/ DMF		Catalyst A	
	TON	TOF	TON	TOF	TON	TOF	TON	TOF
4-Bromoacetophenone	8500	212.5	960	96	32	2	930	2214.3
4-Bromoanisole	32.3	16.2	990	61.9	30	1.9	980	1400
4-lodoanisole	9700	692.8	930	232.5	_	—	890	712
lodobenzene	_	_	980	98	_	—	990	3000
Bromobenzene					31.3	1.9	990	3960

yields were lower. Increasing the reaction temperature in these cases resulted in a small increase in yields (Table 3, entries 10 and 12). The chemoselectivity of the method was investigated using *ortho-*, *meta-* and *para-*bromochlorobenzene as the model substrates. In each case, only Br as the better leaving group was substituted and Cl did not react at all (Table 3, entries 17–20).

To compare the efficiency of this catalyst with other DABCObased catalytic systems, the turnover number (TON) and turnover frequency (TOF) were calculated. As can be seen in Table 4, the TON and TOF of this catalyst were comparable and in some cases even better than in other catalytic systems.

Conclusion

Using readily available and inexpensive materials such as *N*-benzyl DABCO chloride and palladium chloride, we developed an efficient catalytic system for the Suzuki cross-coupling reaction of aryl iodides and bromides at room temperature. The reaction temperature was increased to 100°C for promoting the reaction of less reactive aryl chlorides. Under optimal conditions, for all aryl halides the corresponding coupling products can be achieved in good to high yields.

Experimental

All chemical reagents were purchased from Merck and were used without further purification. ¹H NMR spectra were recorded on a Bruker 500 spectrometer using tetramethylsilane as an internal standard in CDCl₃ or DMSO and FT-IR spectra were obtained as KBr pellets on a JASCO 680-Plus spectrophotometer. Melting points were determined with a Gallenkamp melting apparatus and are uncorrected. Also we used gas chromatography (GC) (BEIFIN 3420 gas chromatograph equipped with a Varian CP SIL 5CB column: 30 m, 0.32 mm, 0.25 μ m) for examination of reactions conversions.

General Procedure for the Synthesis of Palladium Salt (Catalyst A)

To a mixture of 0.25 mmol (0.0597 g) *N*-benzyl DABCO chloride and 0.25 mmol (0.044 g) palladium chloride, 3 ml acetone was added in a round-bottom flask equipped with a condenser and placed in an oil bath under reflux conditions. After 4 h, the reaction mixture was filtered and the resulting solids were washed with water (5 ml) to remove the unreacted *N*-benzyl DABCO chloride. The yellow-brownish catalyst was air-dried and weighed. The yield of catalyst **A** with this procedure was 70%. ¹H NMR (500 MHz, DMSO): δ_{ppm} 3.01 (t, 6H, J = 6.8 Hz, CH₂), 3.29 (t, 6H, J = 6.8 Hz, CH₂), 4.48 (s, 2H, CH₂), 7.48 (br s, 5H, H_{arom}); ¹³C NMR (125 MHz, DMSO): δ_{ppm} 45.67 (C=N_{DABCO}), 52.55 (C=N_{DABCO}), 67.54 (CH₂), 127.96 (C_{arom}), 129.88 (C_{arom}), 131.09 (C_{arom}), 134.08 (C_{arom}); decomp. 298°C. Anal. Calcd for C₂₆H₃₈Cl₆N₄Pd₂: C 37.53, H 4.60, N 6.73. Found: C 37.10, H 4.37, N 6.41.

General Procedure for the Catalyst A-Catalyzed Suzuki–Miyaura Coupling Reaction for Aryl Iodides and Aryl Bromides

A mixture of aryl halide (1 mmol), arylboronic acid (1.2 mmol), K_2CO_3 (2 mmol) and catalyst **A** (0.05 mol%) was added to ethanol (2 ml) and stirred at room temperature (or at 60°C for some substrates) for an appropriate amount of time. After completion of the reaction, as indicated by thin-layer chromatography and GC, the solvent was evaporated. Then, 30 ml water was added to the mixture and the product was extracted with *n*-hexane or ethyl acetate (3 × 10 ml). The organic phase was dried over CaCl₂, concentrated under vacuum and purified by column chromatography on silica gel (*n*-hexane:EtOAc, 9:1).

General Procedure for Catalyst A-Catalyzed Suzuki-Miyaura Coupling Reaction for Aryl Chlorides

A mixture of aryl chloride (1 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (2 mmol), TBAB (0.1 mmol) and catalyst **A** (0.05 mol%) was added to DMF (2 ml). The reaction mixture was stirred in an oil bath at 100°C. After 10 h, the mixture was cooled to room temperature, 30 ml water was added and the product was extracted with *n*-hexane (3 × 10 ml). The organic phase was dried over CaCl₂, concentrated under vacuum and purified by column chromatography on silica gel (*n*-hexane:EtOAc, 9:1).

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