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# (BeDABCO)<sub>2</sub>Pd<sub>2</sub>Cl<sub>6</sub> as an efficient homogeneous catalyst for copper-free Sonogashira cross-coupling reaction

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Abdol R. Hajipour<sup>a</sup>\* and Fatemeh Rafiee<sup>b</sup>

An efficient catalytic system using 1-benzyl-4-aza-1-azoniabicyclo[2.2.2] octane chloride and palladium chloride ((BeDABCO)  $_2Pd_2Cl_6$ ) was developed for the Sonogashira reaction. In the presence of a catalytic amount of this efficient, stable homogeneous catalytic system that is non-sensitive to air and moisture, various aryl halides were efficiently coupled with phenylacetylene in good yields in H<sub>2</sub>O at 50°C under copper-free conditions. Benzyl dabco as an efficient ligand and also a quaternary ammonium salt had an efficient stabilizing effect on the Pd(0) species. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: palladium catalyst; Sonogashira reaction; internal alkynes

### Introduction

Sonogashira coupling reactions acetylenes with aryl or alkenyl halides or triflates have been developed in organic chemistry and material science for the production of internal alkynes and enynes.<sup>[1-7]</sup> Alkynes are used as building blocks for a wide range of pharmaceuticals, natural products, biological active molecules, conducting polymers, nonlinear optical and liquid crystal materials.<sup>[8–10]</sup> Sonogashira cross-coupling reactions are usually mediated by phosphane-based palladium complexes.<sup>[11–13]</sup> Most research has developed to obtain high catalytic activity with efficient catalytic systems. Moreover, a number of important studies have focused on the development of phosphine-free ligands such as N-heterocyclic carbenes.<sup>[14–16]</sup> Phosphine ligands suffer some drawbacks, such as sensitivity to air or moisture, and requirement for an inert environment and large amounts of palladium source for carrying out the reaction. Although carbene ligands are more stable than alkyl phosphines, they must be synthesized through multiple steps. Therefore, designing efficient and phosphine-free ligands remains an important issue.

## **Results and Discussion**

In continuation of our recent investigations on the synthesis and application of palladium catalysts,<sup>[17–23]</sup> we now wish to report the extension of a complex of 1-benzyl-4-aza-1-azoniabicyclo [2.2.2]octane chloride with palladium chloride ((BeDABCO)  $_2$ Pd<sub>2</sub>Cl<sub>6</sub>) as an efficient and highly active homogeneous catalyst for the cross-coupling reaction of various aryl halides with phenylacetylene under copper-free conditions (Scheme 1).

1-Benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride salt ([BeDABCO]Cl) was prepared according to our previous work.<sup>[24]</sup> The reaction of [BeDABCO]Cl with PdCl<sub>2</sub> in 1:1 ratio in acetone reflux gave the (BeDABCO)<sub>2</sub>Pd<sub>2</sub>Cl<sub>6</sub> complex (1).<sup>[25]</sup>

Application of this palladium salt as catalyst for the Sonogashira reaction of various aryl halides with phenylacetylene was examined by optimizing the reaction conditions. We first carried out the coupling reaction between 4-bromobenzonitrile with phenylacetylene as a model reaction. The data showed that the best results were obtained using  $H_2O$  as solvent, piperidine as base and 0.3 mol% of catalyst at 50°C (Table 1). Under these conditions 4-cyanodiphenylacetylene was obtained as the desired product and 1,4-diphenylbuta-1,3-diyne was not formed as a by-product via the homocoupling of phenylacetylene.

These optimized reaction conditions were applied in the Sonogashira cross-coupling reaction of various aryl halides with phenylacetylene (Table 2). We examined the electronic and steric effects on the resulting yields and conversion times of the reactions. Aryl halides substituted with electron-withdrawing groups transformed to the corresponding coupled products rather than electron-donating substituent with better conversion and shorter reaction times. The chemoselectivity of the procedure was examined using 2-, 3- and 4-chlorobromobenzene. In these reactions Br acted as a better leaving group. Aryl chlorides converted to corresponding products more slowly and with lower yields in comparison to the similar aryl iodides and bromides.

The effect of tetraalkylammonium salts on the activity and stability of palladium catalysts has been described by Jeffery,<sup>[26]</sup> in (BeDABCO)<sub>2</sub>Pd<sub>2</sub>Cl<sub>6</sub> catalyst quaternary salt the benzyl dabco as both an efficient ligand and also a quaternary ammonium salt have an efficient stabilizing effect on inhibiting the aggregation of Pd(0) nonstable species.

b Department of Chemistry, Faculty of Science, Alzahra University, Vanak, Tehran, Iran

<sup>\*</sup> Correspondence to: Abdol R. Hajipour, Pharmaceutical Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan 84156, IR Iran. E-mail: haji@cc.iut.ac.ir

a Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan 84156, IR Iran



 $\ensuremath{\textit{Scheme}}$  1. Sonogashira cross-coupling reaction of aryl halides by catalyst (1).

<b>Table 1.</b> Optimization of reaction conditions for the Sonogashiracross-coupling reaction <sup>a</sup>							
Entry Solvent		Base	Catalyst (mol%)	Temperature (°C)	Conversion (%) <sup>b</sup>		
1	NMP	Piperidine	0.4	100	80		
2	DMF	Piperidine	0.4	100	55		
3	CH₃CN	Piperidine	0.4	85	75		
4	EtOH	Piperidine	0.5	65	28		
5	DMAc	Piperidine	0.5	100	45		
6	Dioxane	Piperidine	0.4	90	65		
7	H <sub>2</sub> O	Piperidine	0.4	80	100		
8	H <sub>2</sub> O	Piperidine	0.5	r.t.	40		
9	H <sub>2</sub> O	Piperidine	0.4	50	100		
10	H <sub>2</sub> O	Piperidine	_	50	—		
11	H <sub>2</sub> O	Piperidine	0.3	50	100		
12	H <sub>2</sub> O	Piperidine	0.2	50	90		
13	H <sub>2</sub> O	Pyrrolidine	0.3	50	65		
14	H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	0.3	50	15		
15	$H_2O$	Cs <sub>2</sub> CO <sub>3</sub>	0.3	50	26		
16	H <sub>2</sub> O	NEt <sub>3</sub>	0.3	50	18		
17	H <sub>2</sub> O	DABCO	0.3	50	25		
<sup>a</sup> Reaction conditions: 4-bromobenzonitrile (1 mmol), phenylacetylene (1 mmol), base (2 mmol), solvent (3 ml), catalyst (1) (mol%), 45 min.							

<sup>b</sup>GC yield was determined using *n*-dodecane as an internal standard.

Catalytic Pd(0) species show a positive Hg(0) test, which was assigned as probable evidence for catalysis by Pd nanoparticles. To evaluate the proposed mechanism for producing Pd(0) species, the mercury drop test was used. In the presence of a heterogeneous catalyst, mercury leads to the amalgamation of its surface. In contrast, Hg(0) cannot have a poisoning effect on homogeneous palladium complexes, where the Pd(II) metal centre is tightly bound to the ligand. When a drop of Hg(0) was added to the reaction mixture in all cases under the optimized conditions, no catalytic activity was observed for the catalyst. The obtained data can confirm the Pd(0):Pd(II) cycle.

## Conclusions

In this investigation, a general protocol was applied to the Sonogashira reaction of various aryl halides using (BeDABCO) <sub>2</sub>Pd<sub>2</sub>Cl<sub>6</sub>. Catalytic amounts of this ionic complex converted various aryl halides to the corresponding substituted diphenylacetylenes in good to excellent yields.

Table 2.      Sonogashira cross-coupling reaction using catalyst (1) <sup>a</sup>							
Entry Ar-X		Product <sup>[ref.]</sup>	Yield (%) <sup>b</sup>				
1	Ph-I	Ph—C≡C-Ph <sup>[27]</sup>	96				
2	$p-O_2N-C_6H_4-I$	$p - O_2 N - C_6 H_4 - C \equiv C - Ph^{[28]}$	94				
3	$m-O_2N-C_6H_4-I$	$m - O_2 N - C_6 H_4 - C \equiv C - Ph^{[29]}$	92				
4	p-MeO—C <sub>6</sub> H <sub>4</sub> —I	$p-MeO-C_{6}H_{4}-C\equiv C-Ph^{[30]}$	90				
5	Ph—Br	$Ph - C \equiv C - Ph^{[27]}$	87				
6	p-MeO—C <sub>6</sub> H <sub>4</sub> —Br	$p$ -MeO—C <sub>6</sub> H <sub>4</sub> —C $\equiv$ C-Ph <sup>[30]</sup>	54				
7	p-NC—C <sub>6</sub> H <sub>4</sub> —Br	$p-NC-C_{6}H_{4}-C \equiv C-Ph^{[27]}$	96				
8	$o-O_2N-C_6H_4-Br$	$o - O_2 N - C_6 H_4 - C \equiv C - Ph^{[27]}$	97				
9	<i>p</i> -OHC—C <sub>6</sub> H <sub>4</sub> —Br	$p\text{-OHC}-C_6H_4-C\equiv C\text{-Ph}^{[28]}$	89				
10	<i>p</i> -MeOC—C <sub>6</sub> H <sub>4</sub> —Br	$p\text{-MeOC}-C_6H_4-C\equiv C\text{-Ph}^{[27]}$	74				
11	p-Cl—C <sub>6</sub> H <sub>4</sub> —Br	$p-CI-C_{6}H_{4}-C\equiv C-Ph^{[30]}$	95				
12	m-Cl—C <sub>6</sub> H <sub>4</sub> —Br	$m\text{-}CI\_\_C_6H_4\_\_C\equiv C\_\_Ph^{[31]}$	90				
13	o-Cl—C <sub>6</sub> H <sub>4</sub> —Br	$o-CI-C_{6}H_{4}-C\equiv C-Ph^{[31]}$	60				
14	1-Br—naphthalene	1-(Phenylethynyl)naphthalene <sup>[30]</sup>	50				
15	9-Br—Phenanthrene	9-(phenylethynyl) phenanthrene <sup>[32]</sup>	48				
16	<i>p</i> -O <sub>2</sub> N—C <sub>6</sub> H <sub>4</sub> —Cl	$p - O_2 N - C_6 H_4 - C \equiv C - Ph^{[27]}$	70				
17	2-Br—pyridine	2-(Phenylethynyl)pyridine <sup>[27]</sup>	76				
18 <sup>c</sup>	Ph—Br	$Ph-C \equiv C-CH_2OH^{[33]}$	93				
19 <sup>c</sup>	$p-O_2N-C_6H_4-I$	$p - O_2 N - C_6 H_4 - C \equiv C - C H_2 O H^{[33]}$	90				
20 <sup>c</sup>	<i>p</i> -Cl—C <sub>6</sub> H <sub>4</sub> —Br	$p-CI-C_{6}H_{4}-C \equiv C-CH_{2}OH^{[34]}$	89				

<sup>a</sup>Reaction conditions: aryl halide (1 mmol), phenylacetylene (1 mmol), piperidine (2 mmol), H<sub>2</sub>O (3 ml), catalyst (0.3 mol%), 3 h. <sup>b</sup>Isolated yield after column chromatography.

<sup>c</sup>Reaction conditions: aryl halide (1 mmol), prop-2-yn-1-ol (1 mmol), piperidine (2 mmol), H<sub>2</sub>O (3 ml), catalyst (0.3 mol%), 3 h.

## Experimental

#### General

All melting points were taken using Gallenkamp melting point apparatus. <sup>1</sup>H NMR spectra were recorded using 400 MHz in CDCl<sub>3</sub> solution at room temperature (TMS was used as an internal standard) on a Bruker Avance 500 (Rheinstetten, Germany) and Varian 400 NMR instruments. FT-IR spectra were recorded on a spectrophotometer (Jasco-680, Japan). Spectra of solids were carried out using KBr pellets. Vibrational transition frequencies are reported as a wavenumber (cm<sup>-1</sup>). We used GC (BEIFIN 3420 gas chromatograph equipped a Varian CP SIL 5CB column; 30 m, 0.32 mm, 0.25 µm) for examination of reaction completion and yields. Palladium chloride, aryl halides and all chemicals were purchased from Merck and Aldrich and were used as received.

#### General Procedure for the Sonogashira Cross-Coupling Reaction of Aryl Halides

A mixture of the aryl halide (1 mmol), phenylacetylene (1 mmol), piperidine (2 mmol) and catalyst (1) (0.3 mol%) was added to  $H_2O$  (3 ml) in a round-bottom flask equipped with condenser and heated at 50°C in an oil bath. The mixture was stirred continuously during the reaction and monitored by both TLC and GC. After the reaction was completed, the mixture was cooled to room temperature and diluted with *n*-hexane and water. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure using a rotary evaporator. The residue was purified by silica gel column chromatography.

The substituted diphenylacetylenes synthesized in this work have been reported previously and were characterized by comparing their m.p., and IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra with those found in the literature. $^{[27-34]}$ 

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