

DAB-Cy as an inexpensive and effective ligand for palladium-catalyzed homocoupling reaction of aryl halides

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Abstract

A novel catalytic system of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ with *N,N'*-dicyclohexyl-1,4-diazabutadiene (DAB-Cy) ligand was successfully used in reductive coupling of aryl halides.

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1. Introduction

Biaryls constitute the central skeleton in a great number of natural products and are important pharmacophores in a variety of biologically active compounds [1]. Moreover, by virtue of their excellent physical and chemical properties, they are also widely applied in monomers of conductive polymers [2], chiral host molecules for inclusion compounds [3], and chirality-recognition reagents for chromatography [4]. As for the synthesis of symmetrical biaryls, the main method is the Ullmann reaction [5], however, which requires equimolar amounts of copper and harsh reaction conditions (neat, $>200^\circ\text{C}$). In the last decades, there were notable improvements to the Ullmann reaction. Recently, more and more attentions have been paid in Pd-catalyzed homocoupling reactions [6], which are usually conducted in the presence of the reducing agents, such as zinc [6a,6b,6c], hydrogen gas [6d], formate salts [6e,6f], hydroquinone(HQ) [6g], alcohols [6h,6i,6j,6k,6l] or carbonic oxide gas [6m].

Only $\text{P}(o\text{-tol})_3$, $\text{As}(o\text{-tol})_3$ [6g] and $\text{P}(2\text{-furyl})_3$ [7] had been used as ligands in palladium catalyzed homocoupling reactions. Here, we would like to report the simple *N,N'*-

dicyclohexyl-1,4-diazabutadiene (DAB-Cy) [8] acts as an effective ligand for palladium-catalyzed Ullmann coupling reactions.

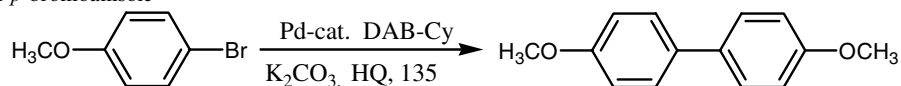
In order to optimize the reaction conditions, we examined the homocoupling of *p*-bromoanisole in different combination and ratios of palladium salts and DAB-Cy. The results are summarized in Table 1. The best result was obtained when the reaction carried out in DMF at 135°C with a ratio of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$: DAB-Cy = 3:4.5 (entry 5). When the reaction carried out at lower temperature, the yield reduced from 86% to 48% (entries 5 and 6). The addition of *n*- Bu_4NBr was essential to the successful transformation (entries 4 and 5). The role of *n*- Bu_4NBr probably strengthened the stabilization of low coordinated Pd(0) species, and was the phase transfer catalyst for the inorganic base/polar solvent/organic substrates/product phases [9].

Under these optimized reaction conditions, we next examined the scope and limitation of this method. The results are summarized in Table 2.

Both electron rich and electron poor aryl bromides could be used to provide the homocoupling products in moderate to good yields. Aryl iodide showed higher reactivity (entry 2). Reductive coupling of 2-bromopyridine (**1n**, entry 14) and 2-bromothiophene (**1p**, entry 16) proceeded smoothly, the coupling product **2n** and **2p** were isolated in 80% and

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Table 1
Homocoupling reaction of *p*-bromoanisole^a



Entry	Catalyst/ligand	Ratio (10 ⁻² mmol)	Temperature (°C)	Yield ^b (%)
1	Pd(OAc) ₂ /DAB-Cy	3/4.5	135	8
2	PdCl ₂ /DAB-Cy	3/4.5	135	18
3	PdCl ₂ (CH ₃ CN) ₂ /DAB-Cy	3/4.5	135	49
4	PdCl ₂ (CH ₃ CN) ₂ /DAB-Cy	4/6	135	50
5 ^c	PdCl ₂ (CH ₃ CN) ₂ /DAB-Cy	3/4.5	135	86
6 ^c	PdCl ₂ (CH ₃ CN) ₂ /DAB-Cy	3/4.5	105	48

^a Reaction conditions: *p*-bromoanisole (1 mmol), K₂CO₃ (1 mmol), HQ (0.5 mmol), DMF (3 ml), 135 °C, 24 h, under the N₂ atmosphere.

^b Isolated yield.

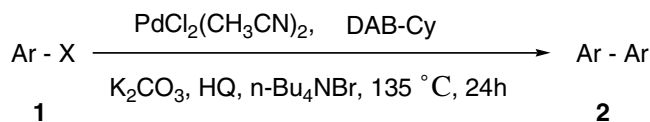
^c Addition of *n*-Bu₄NBr (0.5 mmol).

86% yields, respectively. Under similar conditions, 3-bromopyridine (**1o**, entry 15) and 3-bromothiophene (**1q**, entry 17) were converted into the corresponding reductive coupling products **2o** and **2q** only in moderate yields (67% and 71%, respectively). When electron deficient aryl chloride (**1j**) was used, 21% of biaryl compound was obtained.

However, this catalytic system is sensitive to the steric hindrance. When ortho-substituted aryl bromides (**1e**, **1l**, **1s**) were used, only a trace amount of the desired products were obtained.

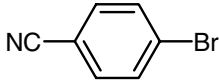
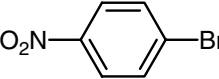
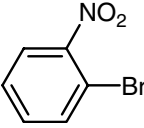
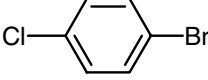
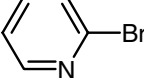
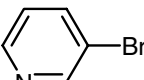
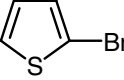
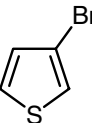
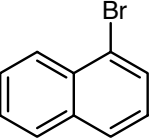
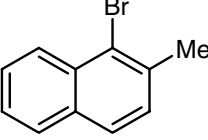
In summary, DAB-Cy is an indeed effective ligand for palladium-catalyzed homocoupling of aryl halides. Both

Table 2
Homocoupling of aryl halides^a



Entry	Aryl halide 1	Yield 2 ^b (%)
1	X = Br	1a 86
2 ^c	X = I	1b 95
3 ^d	X = Cl	1c – ^e
4		1d 70
5		1e trace ^e
6		1f 49
7		1g 71

Table 2 (continued)

Entry	Aryl halide 1		Yield 2 ^b (%)
8	X = Br	1h	86
9 ^d	X = Cl	1i	21
10		1j	86
11		1k	85
12		1l	trace ^e
13		1m	69
14		1n	80
15		1o	67
16		1p	86
17		1q	71
18		1r	76
19		1s	trace ^e

^a Reaction conditions: aryl halide (1 mmol), PdCl₂(CH₃CN)₂ (0.03 mmol), DAB-Cy (0.045 mmol), K₂CO₃ (1 mmol), HQ (0.5 mmol), *n*-Bu₄NBr (0.5 mmol), DMF (3 mL), 135 °C, 24 h, under the N₂ atmosphere.

^b Isolated yield.

^c Temperature is 120 °C, and reaction time is 6 h.

^d PdCl₂(CH₃CN)₂/DAB-Cy is 0.05/0.075 mmol, and reaction time is 48 h.

^e Most of the starting material was recovered.

electron-rich and electron-deficient aryl bromides are applicable substrates to the Pd/ DAB-Cy catalyzed homocoupling reactions.

2. Experimental

2.1. General procedure for symmetrical functionalized biaryls

To a mixture of aryl halide (1 mmol), K_2CO_3 (1 mmol), HQ (0.5 mmol), and *n*-Bu₄NBr (0.5 mmol) was added a DMF solution (3 mL) of $PdCl_2(CH_3CN)_2$ (0.03 mmol) and DAB-Cy (0.045 mmol). The mixture was stirred under nitrogen atmosphere at 135 °C for 24 h. After cooling to room temperature, water and ethyl acetate were added. The organic phase was washed with water and dried over Na_2SO_4 . The solvent was evaporated under vacuum. The biphenyl product was purified by preparative thin layer chromatography.

4,4'-Dimethoxybiphenyl (**2a**) [6g]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.47 (d, 4H, *J* = 8.6 Hz), 6.95 (d, 4H, *J* = 8.6 Hz), 3.84 (s, 6H).

4,4'-Dimethylbiphenyl (**2d**) [8]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.66 (d, 4H, *J* = 8.0 Hz), 7.41 (d, 4H, *J* = 8.0 Hz), 2.56 (s, 6H).

4,4'-(*N,N*-Dimethylamino)biphenyl (**2f**) [9]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.57 (d, 4H, *J* = 8.0 Hz), 7.23 (d, 4H, *J* = 8.0 Hz), 2.42 (s, 12H).

Biphenyl (**2g**) [6g]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.60 (d, 4H, *J* = 7.5 Hz), 7.44 (t, 4H, *J* = 7.2 Hz), 7.35 (t, 2H, *J* = 7.2 Hz).

4,4'-Diacetylbiphenyl (**2h**) [6l]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 8.07 (d, 4H, *J* = 8.4 Hz), 7.72 (d, 4H, *J* = 8.4 Hz), 2.65 (s, 6H).

4,4'-Dicyanobiphenyl (**2j**) [10]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.79 (d, 4H, *J* = 6.5 Hz), 7.70 (d, 4H, *J* = 6.5 Hz).

4,4'-Dinitrobiphenyl (**2k**) [6l]: ¹H NMR (400 MHz, DMSO, TMS) δ 8.36 (d, 4H, *J* = 8.8 Hz), 8.09 (d, 4H, *J* = 8.8 Hz).

4,4'-Dichlorobiphenyl (**2m**) [6l]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.45 (d, 4H, *J* = 10.8 Hz), 7.40 (d, 4H, *J* = 10.8 Hz).

2,2'-Bipyridinyl (**2n**) [6g]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 8.69 (d, 2H, *J* = 4.5 Hz), 8.41 (d, 2H, *J* = 8 Hz), 7.83 (m, 2H), 7.32 (m, 2H).

3,3'-Bipyridinyl (**2o**) [6l]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 8.85 (s, 2H), 8.66 (m, 2H), 7.90 (m, 2H), 7.43 (m, 2H).

2,2'-Bithiophenyl (**2p**) [6l]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.20 (d, 2H, *J* = 4.8 Hz), 7.17 (d, 2H, *J* = 4.8 Hz), 7.01 (m, 2H).

3,3'-Bithiophenyl (**2q**) [6l]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.37 (d, 2H, *J* = 1.4 Hz), 7.34 (m, 4H).

1,1'-Binaphthyl (**2r**) [6g]: ¹H NMR (400 MHz, $CDCl_3$, TMS) δ 7.95 (m, 4H), 7.59 (m, 2H), 7.47 (m, 4H), 7.38 (d, 2H, *J* = 8.3 Hz), 7.28 (m, 2H).

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