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AN EFFICIENT ARYLATION OF BENZOAZOLES WITH ARYL BROMIDES BY A PRACTICAL PALLADIUM-COPPER COCATALYTIC SYSTEM

Xue-Ming Yan,[a,c] Xue-Rong Mao,[a] and Zhi-Zhen Huang*[a,b]

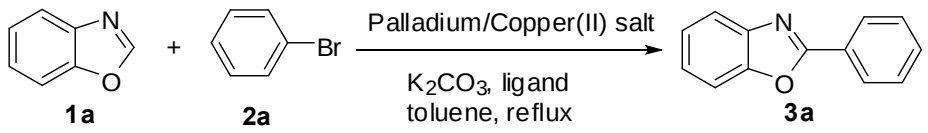
[a]School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, P. R. China, [b]Department of Chemistry, Zhejiang University, Hangzhou 310028, P. R. China, [c]College of Chemistry and Chemical Engineering, University of South China , Hengyang, Hunan 421001, P. R. China

Abstract – A practical, efficient $Pd(OAc)_2$/Cu(II)/PPh_3 cocatalytic system has been developed. With only 1 mol% $Pd(OAc)_2$, 20 mol% copper(II) salt, and 0.5 equiv of inexpensive PPh_3 as ligand, the direct arylation of benzoazoles with aryl bromides could be performed smoothly in mild condition, affording the desired arylated benzoazoles in good yields (75-93%).

Arylated azoles are ubiquitous in natural products and pharmaceuticals, agrochemicals.[1] The transition-metal catalyzed direct arylation of azoles is a powerful strategy for the synthesis of arylated azoles, and has recently received much attentions.[2] In this rapidly growing field, the direct cross-coupling between azoles and aryl halides is a main protocol.[2] As one of the most common arylated azoles, arylated benzoazoles have many biologically important activities.[3] In most cases, the direct arylation of benzoazoles catalyzed by transition-metal required more reactive aryl iodides as arylating reagents.[2b-d] The direct arylation of benzoazoles using aryl bromides, which are cheaper and more commonly used than aryl iodides, did not studied so widely as that using aryl iodides.[4,5] In 2005, Alagille *et al*. disclosed a $Pd(OAc)_2$/Cu(I)Br/P(*t*-Bu)$_3$ cocatalytic system for the direct arylation of benzoazoles with aryl bromides, affording arylated benzoazoles in 8-84% yields.[5a] Very recently, Huang *et al*.[5b] developed an arylation of benzoazoles with aryl bromides by a palladium-copper cocatalytic system, which employed a complicated cocatalytic system: dichlorobis(chloro-di-*tert*-butylphosphine)/Cu(Xantphos)I. Herein we wish to report our recent work on the efficient arylation of benzoazoles with aryl bromides by a practical $Pd(OAc)_2$/Cu(II)/PPh_3 cocatalytic system.

The direct coupling of benzoxazole **1a** with bromobenzene **2a** using K_2CO_3 as a base in toluene was chosen as a model reaction. Initially, various copper salts and $Pd(OAc)_2$ with various N- and P-ligands were probed. It was found that N-ligands such as 1,10-phenanthroline or 2,2-bipyridine led to no desired coupling product (Table 1, entry 1). To our delight, when the inexpensive PPh_3 was used, the coupling reaction performed smoothly with only. 1 mol% $Pd(OAc)_2$ and 20 mol% copper (II) salt such as $Cu(OAc)_2{\cdot}H_2O$ and $CuCl_2{\cdot}2H_2O$ under air, affording the desired arylated benzoxazole **3a** in good yields (Table 1, entries 2 and 3). In the presence of other P-ligands such as $(n\text{-}Bu)_3P$ and bisdiphenylphosphinopropane (DPPP), good yields were also obtained (Table 1, entries 5-8). In contrast, no reaction proceeded in the absence of P-ligands (Table 1, entry 9). The screening of bases revealed that K_2CO_3 was much better than other bases for the reaction (Table 1, entries 10-12). Other palladium catalyst such as $PdCl_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $Pd(dba)_2$ with copper (II) salts can also give the desired product **3a** in good yields (Table 1, entries 13-17). Notably, if either copper or palladium catalyst was present, no arylated product **3a** was obtained under the above standard conditions (Table 1, entries 18, 19).

Table 1. Optimization of Direct Arylation of Benzoxazole[a]



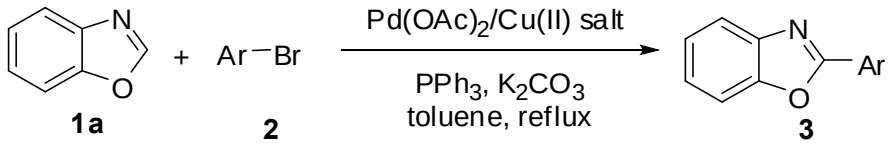
1a **2a** **3a**

Entry	Copper	Palladium	Ligand	Yield[b]
1	Cu(II) salt[c]	$Pd(OAc)_2$	N-ligands[d]	0
2	$CuCl_2{\cdot}2H_2O$	$Pd(OAc)_2$	PPh_3	90
3	$Cu(OAc)_2{\cdot}H_2O$	$Pd(OAc)_2$	PPh_3	92
4	$Cu(acac)_2$	$Pd(OAc)_2$	PPh_3	0
5	$CuCl_2{\cdot}2H_2O$	$Pd(OAc)_2$	$(n\text{-}Bu)_3P$	88
6	$Cu(OAc)_2{\cdot}H_2O$	$Pd(OAc)_2$	$(n\text{-}Bu)_3P$	85
7	$CuCl_2{\cdot}2H_2O$	$Pd(OAc)_2$	DPPP	87
8	$Cu(OAc)_2{\cdot}H_2O$	$Pd(OAc)_2$	DPPP	89
9	Cu(II) salt[c]	Palladium catalyst[g]	-	0
10[e]	$CuCl_2{\cdot}2H_2O$	$Pd(OAc)_2$	PPh_3	0
11[e]	$Cu(OAc)_2{\cdot}H_2O$	$Pd(OAc)_2$	PPh_3	80
12[f]	$CuCl_2{\cdot}2H_2O$	$Pd(OAc)_2$	PPh_3	70
13	$CuCl_2{\cdot}2H_2O$	$PdCl_2$	PPh_3	90
14	$Cu(OAc)_2{\cdot}H_2O$	$PdCl_2$	PPh_3	87
15	$Cu(OAc)_2{\cdot}H_2O$	$Pd(PPh_3)_2Cl_2$	PPh_3	90
16	$Cu(OAc)_2{\cdot}H_2O$	$Pd(PPh_3)_4$	PPh_3	92
17	$Cu(OAc)_2{\cdot}H_2O$	$Pd(dba)_2$	PPh_3	86
18	Cu(II) salt[c]	-	PPh_3	0
19	-	PdX[g]	PPh_3	0

[a]The mixture of **1a** (1.0 mmol), **2a** (1.2 mmol), palladium catalyst (1.0 mol%), copper catalyst (20 mol%), ligand (0.5 equiv), and K_2CO_3 (2.0 equiv) in toluene(3 mL) was refluxed for 3h under air. [b]Isolated yields(%). [c]Cu(II) salt: $Cu(OAc)_2{\cdot}H_2O$, $CuCl_2{\cdot}2H_2O$ et al [d]N-ligands =1,10-phenanthroline or 2,2-bipyridine. [e]Cs_2CO_3 was used as base. [f]$K_3PO_4{\cdot}3H_2O$ was used as base. [g]Palladium catalysts listed in the table.

After screening of various copper and palladium catalysts, ligands, bases etc, it can be concluded that the optimized reaction should be performed by the cocatalytic system of 1 mol% $Pd(OAc)_2$ and 20 mol% $Cu(OAc)_2{\cdot}H_2O$ or $CuCl_2{\cdot}2H_2O$ in the presence of PPh_3 (0.5 equiv) and K_2CO_3 (2.0 equiv). Under the optimal reaction conditions, a series of aryl bromides **2a-l** were examined in the coupling reaction. It was found that the aryl bromides bearing either electron-donating or withdrawing groups on benzene rings **2a-i** could perform the coupling reaction smootly with benzoxazole **1a** under air, furnishing the desired arylated benzoxazole **3a-i** in good yields (Table 2, compare entries 1-10). Heteroaryl bromides **2k-l** were also good coupling partners, giving the biheteroarenes **3k-l** in good yields (Table 2, entries 11, 12).

Table 2. Direct Arylation of Benzoxazole **1a** with Aryl Bromides **2**[a]

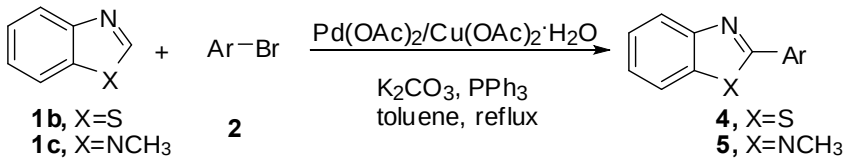


1a **2** **3**

Entry	Ar	Product **3**[b]	Yield (%)[c]	Yield (%)[d]
1	C_6H_5	**3a**[7a]	93	92
2	4-$MeOC_6H_4$	**3b**[7b]	88	91
3	3-$MeOC_6H_4$	**3c**[7b]	90	89
4	4-MeC_6H_4	**3d**[7c]	92	86
5	3-MeC_6H_4	**3e**[7c]	84	89
6	3,5-$Me_2C_6H_3$	**3f**[7b]	91	88
7	2-$MeOC_6H_4$	**3g**[7b]	81	80
8	4-FC_6H_4	**3h**[7a]	83	82
9	4-ClC_6H_4	**3i**[7a]	87	83
10	naphthalen-1-yl	**3j**[7b]	83	85
11	pyridin-3-yl	**3k**[7b]	80	84
12	pyridin-2-yl	**3l**[7b]	80	77

[a]The mixture of **1a** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (1.0 mol%), copper (II) salt (20 mol%), PPh_3 (0.5 equiv), and K_2CO_3 (2.0 equiv) in toluene (3 mL) was refluxed for 3 h under air. [b]Isolated yields. [c]$Cu(OAc)_2{\cdot}H_2O$ was used as cocatalyst. [d]$CuCl_2{\cdot}2H_2O$ was used as cocatalyst.

Table 3. Direct Arylation of Benzothiazoles **1b** or Benzoimidazoles **1c** with Aryl Bromides **2**[a]



1b, X=S
1c, X=NCH_3
2
4, X=S
5, X=NCH_3

Product	Ar	Yield (%)[b]	Product	Ar	Yield (%)[b]
4a[5b]	C_6H_5	86	**4i**[4c]	pyridin-3-yl	79
4b[4c]	4-$MeOC_6H_4$	92	**5a**[7b]	C_6H_5	80
4c[4c]	3-$MeOC_6H_4$	83	**5b**[7a]	4-$MeOC_6H_4$	85
4d[5b]	4-MeC_6H_4	84	**5c**[7b]	3-$MeOC_6H_4$	81
4e[5b]	3-MeC_6H_4	82	**5d**[7a]	4-MeC_6H_4	83
4f[5b]	3,5-$Me_2C_6H_3$	92	**5e**[7a]	3-MeC_6H_4	77[c]
4g[5b]	4-FC_6H_4	81	**5f**[7a]	3,5-$Me_2C_6H_3$	75
4h[4c]	naphthalen-1-yl	77	-	-	-

[a]The mixture of **1b** or **1c** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (1.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), PPh_3 (0.5 equiv), and K_2CO_3 (2.0 equiv) in toluene (3 mL) was refluxed for **1b** 6 h or for **1c** 10 h. [b]Isolated yields. [c]$CuCl_2{\cdot}2H_2O$ was used as cocatalyst.

Moreover, benzothiazole **1b** and benzoimidazole **1c** were also tested in the coupling reaction using $Pd(OAc)_2/Cu(OAc)_2{\cdot}H_2O/PPh_3$ as a cocatalytic system. It was found that both benzothiazole **1b** and benzoimidazole **1c** could react smoothly with various aryl bromides **2** to give the desired arylated products **4** and **5** in moderate to good yields (Table 3). Compared with benzoxazole **1a**, benzothiazole **1b** and benzoimidazole **1c** were less reactive and required longer reaction time (3 h for **1a**, 6 h for **1b** and 10h for **1c**), probably because the acidities of H-2 in **1b** and **1c** are weaker than that in **1a**.[6]

In summary, a practical $Pd(OAc)_2/Cu(II)/PPh_3$ cocatalytic system has been developed for the direct arylation of benzoazoles **1a**, benzothiazole **1b** or benzoimidazole **1c** with various aryl bromides **2**. The yields (75-93%) are better than that using $Pd(OAc)_2/Cu(I)Br/P(t\text{-}Bu)_3$.[5a] This synthetic reaction also has the advantages of readily available catalysts, low palladium catalyst loading, mild reaction conditions, and simple manipulations.

EXPERIMENTAL

General procedure for the arylation of benzoazoles **1a-c** with aryl bromide **2**: The reaction mixture of benzoazoles **1a-c** (1.0 mmol), aryl bromide **2** (1.2 mmol), $Pd(OAc)_2$ (2.2 mg, 1.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ or $CuCl_2{\cdot}2H_2O$ (20 mol%), and K_2CO_3 (2.0 equiv, 0.276 g) in toluene (3 mL) was refluxed for 3-10 h. Then, the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ EtOAc as eluent) to give arylated benzoxazole **3-5** (All the coupling products **3a**[7a],**b**[7b],**c**[7b],**d**[7c],**e**[7c],**f**[7b],**g**[7b],**h**[7a],**i**[7a],**j**[7b],**k**[7b],**l**[7b]; **4a**[5b],**b**[4c],**c**[4c],**d**[5b],**e**[5b],**f**[5b],**g**[5b],**h**[4c],**i**[4c]; **5a**[7b],**b**[7a],**c**[7b],**d**[7a],**e**[7a],**f**[7a] are known compounds).

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