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Copper and Iron-assisted Palladium-catalyzed Direct Arylation of Azoles with Arylboronic Acids under Ligand and Base-free Conditions

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Abstract: The direct arylation of azoles with arylboronic acids is effectively promoted by $PdCl_2$ in the presence of copper and iron salts under ligand and base-free conditions. This reaction can be applied to heterocycles such as benzothiazole, benzoxazole, 1-methylbenzimidazole and 4,5-dimethylthiazole with moderate to good yields.

Keywords: Palladium, copper, iron, arylation, arylboronic acid.

INTRODUCTION

Aryl-azoles such as aryl-substituted benzothiazoles, benzoxazoles and benzimidazoles represent a predominant structural motifs in a wide array of biologically important natural products and synthetic pharmaceuticals [1]. Moreover, they have also found applications in organic functional materials like fluorescent dyes and liquid crystals [2]. Therefore, the development of efficient synthesis of aryl-substituted azoles and their derivatives have stimulated consideration interest. The typical approaches to prepare these important compounds involve either the metal-catalyzed intramolecular cyclization of thioanilides (or 2-haloanilides) or the condensation of 2-aminophenol (or 2-aminothiophenol) with carboxylic acid derivatives or aldehydes [3]. As a variety of transition metal-mediated C-C bond formations through aromatic C-H activation directly have received significant attention owing to its advantage in atom efficiency compared to traditional cross-couplings [4], aryl-substituted azoles prepared by direct arylation of heterocycles through metal-catalyzed C-H bond activation with aryl halides [5], aromatic carboxylic acids [6], arylsilanes [7], aldehydes [8], and sodium arylsulfinates [9] have also attracted attention recently. In addition, a few successful examples of the coupling of azoles with arylboronic acids have also been described so far [10-13], however, these protocols generally require the stoichiometric amount of base which may facilitate the homocoupling of arylboronic acid and organic ligands or additives which make it difficult for the separation and purification after the reactions. Consequently, considering the preference of modern green chemistry, the development of an efficient ligand and base-free reaction system is still highly desirable. Herein, we describe a simple and practical synthetic pathway to achieve the direct C-H bond functionalization of benzothiazole, benzoxazole, 1-methylbenzimidazole and 4,5-dimethylthiazole with arylboronic acids by transition-metal catalysts under ligand and base-free conditions.

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RESULTS AND DISCUSSION

We undertook an intensive screening process using benzothiazole and phenylboronic acid as model substrates. According to the literature [10-13], the reaction conditions may require an oxidant to regenerate the Pd catalyst, so $Cu(OAc)_2$ was initially used to play as the role in the model reaction. In the presence of 10 mol% of $Pd(OAc)_2$ as the catalyst and 1 equiv of $Cu(OAc)_2$ as the oxidant in DMSO at 120°C for 24h, to our delight, 2-phenylbenzothiazole was isolated in 30% yield (Table **1**, entry 1). At the same time, substantial amount of biphenyl resulted from consumption of phenylboronic acid and small amount of bibenzothiazole resulted from the undesired homocoupling of benzothiazole were determined by gas chromatography. As the palladium sources, the comparable product yields were obtained when $PdCl_2$ and $Pd(MeCN)_2Cl_2$ were used as the catalyst whereas a lower yield was afforded when Pd/C was used instead of $Pd(OAc)_2$ (entries 2-4). In the absence of Pd, a majority of benzothiazole were recovered from the reaction system and a small amount of unexpected product through ring-opening arylation (2-aminophenyl sulfide) was detected (entry 5). So $PdCl_2$ was chosen as catalyst in the following investigation due to its low cost. Various Cu(II) salts, such as $CuSO_4$, $CuCl_2$ and CuO were also examined as oxidants for this direct arylation reaction, and $Cu(OAc)_2$ was the best choice obviously (entries 6-8). However, other oxidants like $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were no longer effective in the reaction (entry 9).

Then the effect of additive on this reaction was also investigated to improve our low reaction yield. Inspired by results reported by Georg *et al.* that the addition of $CuCl_2$ can effectively enhance the direct arylation reaction of enaminone and arylboronic acid [14], we tried to employ the copper salts for our model reaction. Encouragingly, when 0.5 equiv $CuCl_2$ was used, the yield was increased obviously. And other chloride salts like $FeCl_3$, $CeCl_3$ and $NiCl_2$ were also examined, $FeCl_3$ was proved to be the best efficient additive and the yield of target compound was increased upon to 65% (entries 10-14). Among the solvents tested, DMF was found to be more effective than other solvents such as

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Table 1. Optimization of the Direct Arylation Conditions[a]

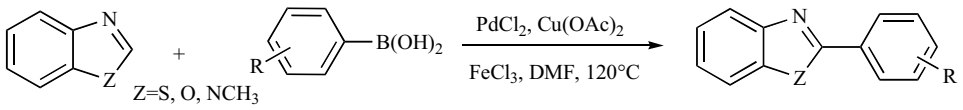
Entry	Pd Catalyst [mol%]	Oxidant [equiv]	Additive [equiv]	Solvent	Yield(%)[b]
1	$Pd(OAc)_2$(10)	$Cu(OAc)_2$(1)	/	DMSO	30
2	$PdCl_2$(10)	$Cu(OAc)_2$(1)	/	DMSO	32
3	$Pd(MeCN)_2Cl_2$(10)	$Cu(OAc)_2$(1)	/	DMSO	27
4	Pd/C(10)	$Cu(OAc)_2$(1)	/	DMSO	12
5	/	$Cu(OAc)_2$(1)	/	DMSO	0
6	$PdCl_2$(10)	$CuSO_4$(1)	/	DMSO	22
7	$PdCl_2$(10)	$CuCl_2$(1)	/	DMSO	30
8	$PdCl_2$(10)	CuO(1)	/	DMSO	12
9	$PdCl_2$(10)	$K_2S_2O_8$(1)	/	DMSO	<5
10	$PdCl_2$(10)	$Cu(OAc)_2$(1)	$CuCl_2$(0.5)	DMSO	55
11	$PdCl_2$(10)	$Cu(OAc)_2$(1)	CuCl(0.5)	DMSO	48
12	$PdCl_2$(10)	$Cu(OAc)_2$(1)	$FeCl_3$(0.5)	DMSO	65
13	$PdCl_2$(10)	$Cu(OAc)_2$(1)	$CeCl_3$(0.5)	DMSO	18
14	$PdCl_2$(10)	$Cu(OAc)_2$(1)	$NiCl_2$(0.5)	DMSO	15
15	$PdCl_2$(10)	$Cu(OAc)_2$(1)	$FeCl_3$(0.5)	DMF	80
16	$PdCl_2$(10)	$Cu(OAc)_2$(1)	$FeCl_3$(0.5)	DMA	76
17	$PdCl_2$(10)	$Cu(OAc)_2$(1)	$FeCl_3$(0.5)	NMP	72
18	$PdCl_2$(10)	$Cu(OAc)_2$(1)	$FeCl_3$(0.5)	CH_3CN	45
19	$PdCl_2$(5)	$Cu(OAc)_2$(1)	$FeCl_3$(0.5)	DMF	75
20	$PdCl_2$(20)	$Cu(OAc)_2$(1)	$FeCl_3$(0.5)	DMF	76
21	$PdCl_2$(10)	$Cu(OAc)_2$(0.5)	$FeCl_3$(0.5)	DMF	81
22	$PdCl_2$(10)	$Cu(OAc)_2$(1.5)	$FeCl_3$(0.5)	DMF	78
23	$PdCl_2$(10)	$Cu(OAc)_2$(0.5)	$FeCl_3$(1)	DMF	79
24	$PdCl_2$(10)	$Cu(OAc)_2$(0.5)	$FeCl_3$(0.3)	DMF	70
25	$PdCl_2$(10)	/	$FeCl_3$(0.5)	DMF	<5
26[c]	$PdCl_2$(10)	$Cu(OAc)_2$(0.5)	$FeCl_3$(0.5)	DMF	55

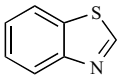
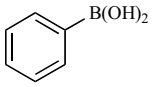
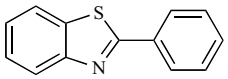
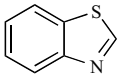
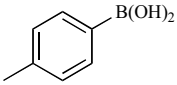
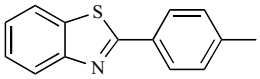
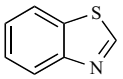
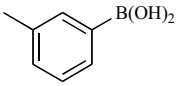
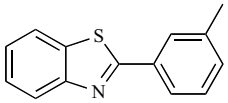
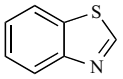
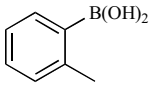
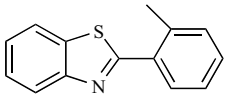
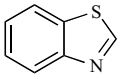
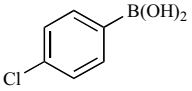
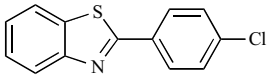
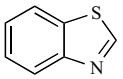
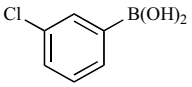
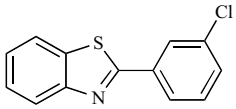
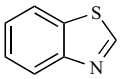
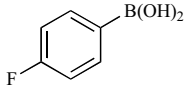
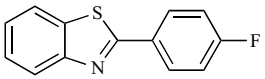
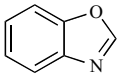
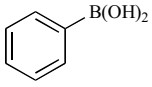
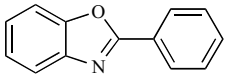
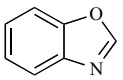
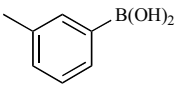
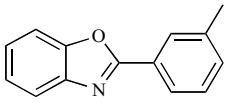
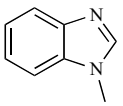
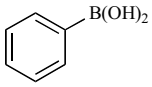
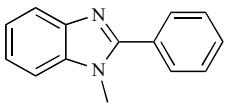
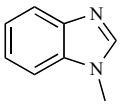
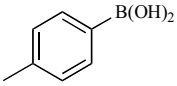
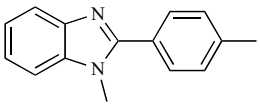
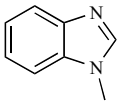
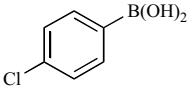
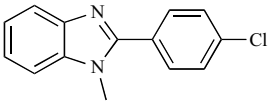
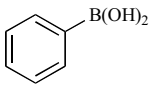
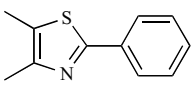
[a] Reaction conditions: benzothiazole (0.5 mmol); phenylboronic acid (1.0 mmol); solvent (2.0 mL); 120°C, 24h, in air. [b] Isolated yield. [c] Phenylboronic acid (0.5 mmol).

DMSO, NMP and CH_3CN, to afford 2-phenylbenzothiazole in 80% yield (entries 15-18). Further experiments showed that decreasing the catalyst loading from 10 to 5 mol% resulted in the decrease of the yield even under extended reaction time conditions. In contrast, no significant improvement of the yield was observed by increasing the catalyst loading to 20 mol%. With respect to the amount of oxidant and additive used in the reaction, 0.5 equiv $Cu(OAc)_2$ and 0.5 equiv $FeCl_3$ were found to be optimal (entries 19-24). The control experiment also showed that $Cu(OAc)_2$ was necessary for the reaction to proceed (entry 25). In addition, decreasing the amount of phenylboronic acid to 1 equiv resulted in a poor yield due to the formation of biphenyl in a significant amount even under the optimal conditions (entry 26). Thus, the best result was obtained by using 0.5 equiv of $Cu(OAc)_2$ as the oxidant, 0.5 equiv of $FeCl_3$ as the additive in the presence of 10 mol% $PdCl_2$ in DMF at 120°C for 24h.

The direct arylation between benzothiazole with various arylboronic acids was investigated under the optimal conditions and the results are shown in Table **2**. For arylboronic acids with different functional groups, including methyl, methoxy, fluoro, and chloro groups on the para- or meta-position of benzene rings, could react with benzothiazole smoothly to generate the desired products in moderate to good yields (Table **2**, entries 1-7). Even arylboronic acid with the steric hindrance substituent at ortho position was tolerated in this reaction (entry 4). Remarkably, fluorobiaryl products are popular in medicinal and materials chemistry, and chloro-substituted benzothiazole would allow for further

Table 2. Direct Arylation of Azole with Various Arylboronic Acids[a]



Entry	Azole	Arylboronic Acids	Product	Yield(%)[b]	Ref.
1				81	[8]
2				78	[8]
3				72	[5b]
4				53	[8]
5				68	[8]
6				70	[8]
7				65	[8]
8				85	[5b,9]
9				78	[9]
10				75	[5b]
11				72	[5a]
12				65	[5a]
13				77	[5i]
14				75	[9,12]

[a] Reaction conditions: azole (0.5 mmol); arylboronic acid (1.0 mmol); $PdCl_2$ (0.05mmol); $Cu(OAc)_2$ (0.25 mmol); $FeCl_3$ (0.25 mmol); DMF (2.0 mL); 120 °C, 24 h, in air. [b] Isolated yield.

derivatization through cross-coupling reactions such as Heck, Suzuki and Ullmann reactions, to feature the utility of this protocol.

We then investigated the reaction of other heterocycles such as benzoxazole, 1-methylbenzimidazole and 4,5-dimethylthiazole with arylboronic acids. Similar to the arylation of benzothiazole, various substituted arylboronic acids successfully reacted with heterocycles to afford the corresponding aryl-substitued azoles under the present reaction conditions (entries 8-14). The yields for the arylation of 1-methylbenzimidazole were a little lower than that for benzothiazole and benzoxazole, which may arise from the different acidities of hydrogen at C-2 of heterocycles and is consistent with the previous report [5a].

In summary, $PdCl_2$ in conjunction with copper and iron salts can effectively catalyze the arylation of the C-H bond of heterocycles, such as benzothiazole, benzoxazole, 1-methylbenzimidazole and 4,5-dimethylthiazole under ligand and base-free conditions, to form the corresponding heterocycle compounds in moderate to good yields. The extend investigation of this kind reaction and mechanism is underway in our laboratory.

EXPERIMENTAL

General

All commercial reagents were used as received without purification, and all solvents were of reagent grade. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz with Bruker Avance 300 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Melting points were obtained from a XT4A melting point apparatus and were uncorrected. Gas chromatography mass spectra (GC/MS) were recorded on an Agilent Technologies 6890 N instrument with an Agilent 5975 N mass detector (EI) and a HP5-MS 30 m×0.25 mm capillary apolar column.

General Experimental Procedure

Azole (0.5 mmol), arylboronic acid (1.0 mmol), $PdCl_2$ (0.05 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.25 mmol), $FeCl_3$ (0.25 mmol) and DMF (2.0 mL) were taken in a 25 mL two-neck flask. The mixture was heated at 120 °C in air for 24 h by magnetic stirring. After cooling to room temperature, the product was diluted with H_2O (5 mL) and extracted with EtOAc (4×15 mL). The extracts were combined and washed by brine (3×10 mL), dried over $MgSO_4$, filtered, and evaporated, and purified by chromatography on silica gel to obtain the desired products with ethyl acetate/hexane (v/v=1:1~1:10). The products were characterized by their spectral and analytical data and compared with those of the known compounds.

Characterization Data of All the Products

2-Phenylbenzothiazole[8]

White solid, mp 97-99°C (lit.: 98.1-100.7°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.42 (m, 1H), 7.48-7.50 (m, 4H), 7.90-7.92 (m, 1H), 8.07-8.11 (m, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 121.6, 123.2, 125.2, 126.3, 127.5, 129.0, 130.9, 133.6, 134.9, 154.0, 168.0; GC-MS (EI, m/z): 211 [M^+].

2-(4-Methylphenyl)benzothiazole[8]

Yellow solid, mp 110-112°C (lit.: 110.3-112.7°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.28-7.39 (m, 3H), 7.45-7.50 (m, 1H), 7.87-8.07 (m, 4H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 21.5, 121.5, 123.0, 125.0, 126.2, 127.5, 129.7, 130.9, 134.9, 141.4, 154.1, 168.2; GC-MS (EI, m/z): 225 [M^+].

2-(3-Methylphenyl)benzothiazole[5b]

Yellow solid, mp 69-70°C (lit.: 71.5°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.25-7.40 (m, 3 H), 7.46-7.52 (m, 1H), 7.85-7.94 (m, 3 H), 8.06-8.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 21.3, 121.5, 123.2, 124.8, 125.1, 126.2, 128.0, 128.9, 131.8, 133.5, 135.0, 138.8, 154.1, 168.3; GC-MS (EI, m/z): 225 [M^+].

2-(2-Methylphenyl) benzothiazole[8]

Yellow solid, mp 55-57°C (lit.: 56.2-57.7°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H), 7.31−7.51 (m, 5H), 7.75 (d, J = 7.0 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 21.3, 121.3, 123.3, 125.0, 126.0, 126.1, 129.9, 130.5, 131.5, 133.1, 135.5, 137.2, 153.7, 167.9; GC-MS (EI, m/z): 225 [M^+].

2-(4-Chlorophenyl)benzothiazole[8]

White solid, mp 109-110°C (lit.: 110.3-112.5°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.53(m, 4H), 7.89-8.08 (m, 4H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 121.6, 123.2, 125.4, 126.5, 128.7, 129.2, 132.0, 135.0, 137.0, 154.0, 166.6; GC-MS (EI, m/z): 245 [M^+].

2-(3-Chlorophenyl)benzothiazole[8]

White solid, mp 112-114°C (lit.: 112.3-114.2°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.51 (m, 4H), 7.90-8.12 (m, 4H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 121.7, 123.4, 125.5, 125.6, 126.5, 127.3, 130.2, 130.8, 135.0, 135.1, 135.2, 153.9, 166.2; GC-MS (EI, m/z): 245 [M^+].

2-(4-Fluorophenyl)benzothiazole[8]

White solid, mp 109-111°C (lit.: 110.1-112.6°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16-7.26 (m, 3H), 7.39-7.42 (m, 1H), 7.47-7.50 (m, 1H), 7.89-7.92 (m, 1H), 8.05-8.12 (m, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 116.0, 116.3, 121.6, 123.2, 125.2, 126.4, 129.5, 129.6, 135.0, 154.0, 164.4, 166.7; GC-MS (EI, m/z): 229 [M^+].

2-Phenylbenzoxazole[5b, 9]

White solid, mp100-102°C (lit.: 102.8°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.27 (m, 1H), 7.35-7.38 (m, 2H), 7.53-7.61 (m, 3H), 7.79-7.80 (m, 1H), 8.27-8.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 110.6, 120.0, 124.5, 125.1, 127.2, 127.6, 128.9, 131.5, 142.1, 150.7, 163.1; GC-MS (EI, m/z): 229 [M^+].

2-(3-Methylphenyl) benzoxazole[9]

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 7.26 (s, 1H), 7.34-7.40 (m, 3H), 7.57-7.58 (m, 1H), 7.76-7.80 (m, 1H), 8.05-8.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 21.3,

110.5, 119.9, 124.5, 124.8, 125.0, 128.2, 128.8, 132.3, 138.7, 142.1, 150.7, 163.2; GC-MS (EI, m/z): 229 [M^+].

2-Phenyl-1-methyl-1H-benzo[d]imidazole[5b]

White solid, mp 92-94°C (lit.: 94.7°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 7.30-7.37 (m, 2H), 7.38-7.42 (m, 1H), 7.48-7.57 (m, 3H), 7.75-7.80 (m, 3H), 7.80-7.88 (m, 1H). ^{13}C NMR ($CDCl_3$, 75MHz): δ 31.7, 109.6, 119.9, 122.4, 122.7, 128.7, 129.5, 129.7, 130.2, 136.6, 143.0, 153.8.

2-(p-Tolyl)-1-methyl-1H-benzo[d]imidazole[5a]

White solid, mp 125-127°C (lit.: 127-128°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.87 (s, 3H), 7.30-7.40 (m, 5H), 7.65-7.68 (m, 2H), 7.82-7.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 21.5, 31.7, 109.6, 119.6, 122.5, 122.6, 127.3, 129.3, 129.4, 136.6, 140.0, 142.5, 153.9; GC-MS (EI, m/z): 223 [M^+].

2-(4-Chlorophenyl)-1-methyl-1H-benzo[d]imidazole[5a]

White solid, mp 111-113°C (lit.: 112-113°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H), 7.33-7.49 (m, 5H), 7.65-7.67 (m, 1H), 7.80-7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 31.6, 109.7, 120.0, 122.7, 123.2, 127.5, 129.5, 129.8, 129.9, 134.8, 136.5, 142.8, 152.5; GC-MS (EI, m/z): 243 [M^+].

4,5-Dimethyl-2-phenylthiazole[5i]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 6H), 7.26-7.42 (m, 3H), 7.87-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 11. 5, 14.8, 126.1, 126.5, 128.7, 129.3, 133.9, 149.2, 163.3; GC-MS (EI, m/z): 189.

4,5-Dimethyl-2-(4-methylphenyl)thiazole[9,12]

Colorless solid, mp 56-58°C (lit.:56-57°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 9H), 7.20 (d, J = 7.8 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 11.4, 14.7, 21.3, 125.9, 126.1, 129.4, 131.3, 139.4, 149.0, 163.5; GC-MS (EI, m/z): 203 [M^+].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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