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Rhodium-catalyzed direct oxidative cross-coupling of 2-aryl pyridine with benzothiazoles

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ABSTRACT

A rhodium-catalyzed cross-coupling reaction of 2-aryl pyridine and benzothiazoles via dual C–H bond functionalization has been developed in the presence of copper salts. The reaction system provides a new approach to heterobiaryl species, which are ubiquitous in pharmaceuticals and nature products.

1. Introduction

Heterobiaryl species are usually very important compounds in biological, pharmaceutical, and material sciences due to the construction of backbone of pharmaceuticals and nature products. The traditional method for synthesis of these compounds is cross-coupling reactions of aryl halides with heteroarylmetals or arylmetals with heteroaryl halides catalyzed by different metals.[1] In the past decades, several efficient catalytic systems have been developed in the direct arylation of heterocycle C–H bonds with aryl halides employing Pd,[2] Rh,[3] Ru,[4] Ir,[5] Fe,[6] Co,[7] Ni,[8] and Cu.[9] A more efficient protocol for the synthesis would be cross-dehydrogenative-coupling of arenes and heteroarenes directly by using palladium,[10] copper,[11] rhodium,[12] and ruthenium[13] as the catalyst. In these cases, several heteroarene derivatives have been studied to achieve this goal, such as oxazoles,[14] thiazoles,[15] imidazoles,[16] furans,[17] thiophenes,[18] pyrroles.[19]

Among these research, Miura and co-workers developed C–H functionalization of 2-aryl pyridine with benzoxazole in the presence of copper salt in good yields.[14a] You's group realized this transformation by using $(RhCp^*Cl_2)_2$ as the catalyst in the presence of copper salt.[12j] In continuing our efforts in transition metal-catalyzed C–H functionalization,[20] herein, we report rhodium (II) acetate catalyze direct cross-dehydrogenative-coupling reaction of 2-aryl pyridine with benzothiazoles in the presence of $Cu(OAc)_2$ (Fig. 1).

2. Results and discussion

Initially, the cross-coupling reaction of 2-phenylpyridine (**1a**) with benzothiozole (**2a**) was carried out in the presence of 3 equiv $Cu(OAc)_2$ in *N*,*N*-dimethylacetamide (DMA) at 160 °C for 9 h under an argon atmosphere, forming the desired product (**3aa**) in 15% yields (Table 1, entry 1). Interestingly, while catalytic rhodium acetate dimmer and Xantphos (entry 4) were used in the system, the yield was increased to 42%. The other ligands (entries 5–7) also could improve the reactivity of rhodium species and the best ligand is triphenylphosphine (entry 7). Usually, CuI is an efficient reagent in the coupling reaction of benzothiozoles,[21] which was chosen as an additive. It was found that 0.5 equiv CuI was employed in this reaction under former conditions to obtain the product **3aa** in 81% yield (entry 11). While the amount of CuI was increased to 1 equiv the yield could be achieved to 90% without diheteroarylated product, which showed the good regioselectivity and higher yield compared with the literature.[14a] (entry 12). Whereas only 30% yield was obtained in the reaction using CuCl as the additive (entry 13). It was shown that the $Cu(OAc)_2$ was necessary for the reaction since the absence of $Cu(OAc)_2$ induced the decrease of the yield (58%) even 1 equiv CuI was added under the conditions (entry 14). Moreover, the reaction could not carry out without two copper salts using rhodium acetate as the catalyst (entry 15).

With a highly active catalytic system in hand, the scope of 2-phenylpyridines was investigated. As expected, a variety of substituted 2-phenylpyridines **1** were reacted with

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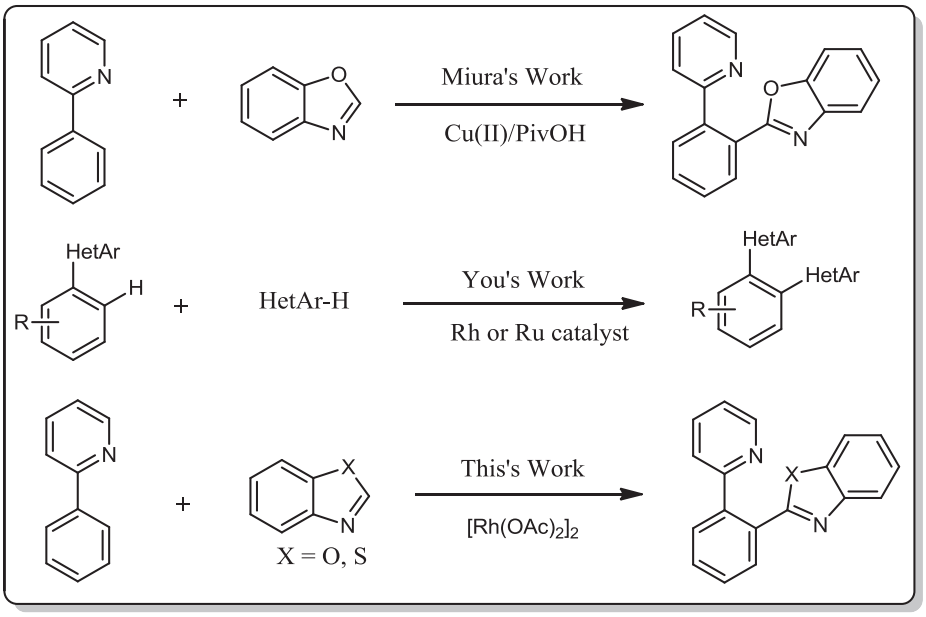
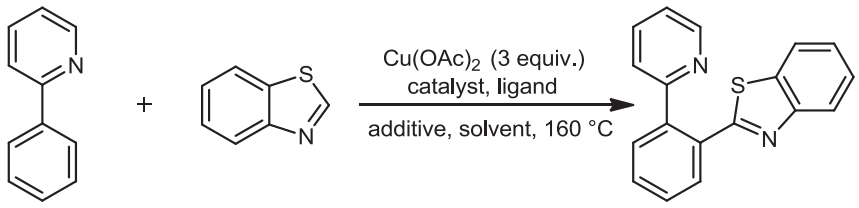


Fig. 1. The work on dehydrogenative cross-coupling of heteroarenes.

Table 1
Optimization of the reaction conditions[a]



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

Entry	Cat. (mol %)	L (mol %)	Additive	Solvents	Yield (%)[b]
1				DMA	15
2	$Pd(OAc)_2$ (10)	Xantphos[c] (20)		DMA	0
3	$RhCl(PPh_3)_3$ (10)			DMA	18
4	$[Rh(OAc)_2]_2$ (5)	Xantphos (20)		DMA	42
5	$[Rh(OAc)_2]_2$ (5)	1,10-Phenanthroline (20)		DMA	34
6	$[Rh(OAc)_2]_2$ (5)	2,2′-Bipyridine (20)		DMA	24
7	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)		DMA	53
8	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)		Mesitylene	17
9	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)		DMSO	46
10	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)		DMF	36
11	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)	CuI(0.5)	DMA	81
12	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)	CuI(1)	DMA	90
13	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)	CuCl(1)	DMA	30
14	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)	CuI(1)	DMA	58[d]
15	$[Rh(OAc)_2]_2$ (5)	PPh_3 (20)		DMA	Trace[e]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst, copper acetate (0.6 mmol), additive, solvent (2.0 mL), 160 °C, 9 h.
[b] Yield after purification.
[c] 4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9*H*-xanthene.
[d] Without 3 equiv $Cu(OAC)_2$.
[e] Without $Cu(OAc)_2$ and CuI.

benzothiazole **2a** to evaluate the substitution effects in 2-phenylpyridine. The electro-rich substituent on the aryl ring of 2-aryl pyridine showed good reactivities in the reaction. 94% Yield of products could be achieved using 2-(4-methoxyphenyl) pyridine **1e** as the substrate (Table 2, entry 5). In contrast, electro-deficient substituent on the aryl ring of 2-aryl pyridine hindered the reaction, which induced to form moderate yield of corresponding product (entries 7–9). Fortunately, the chloro group was compatible with the reaction conditions in 62% yield (entry 10).

Next, various benzothiazole derivatives worked well under the optimal conditions. A range of functional groups could be tolerated in this reaction, such as alkyl, methoxy, chloro, nitro, and ester group. Among these cases, the electro-rich substituent on the phenyl ring of benzothiozoles benefited from the reaction (Table 3, entries 1 and 2), whereas the electro-deficient substituents affected the reaction efficient (entries 3 and 4). However, the reaction was turned less active while the substituted benzothiazole with nitro group (entry 5) was employed in the transformation. Unfortunately, benzoxazole was not a nice substrate under the