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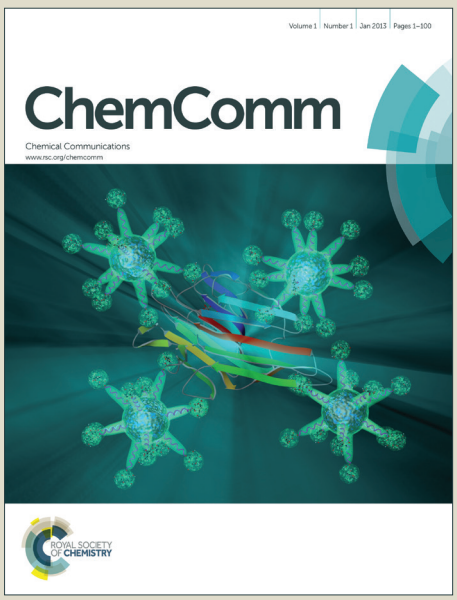

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Palladium-catalyzed Oxidative CH/CH Cross-coupling of Pyridine *N*-oxides with Five-membered Heterocycles

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Using Ag_2CO_3 as an additive, we developed the Pd-catalyzed intermolecular C–H/C–H cross-coupling between pyridine *N*-oxides with five-membered heterocyles such as 1-benzyl-1,2,3-triazoles, thiophens and furans. This protocol provides an efficient and regioselective approach for the synthesis of unsymmetrical biheteroaryl molecules

A heteroaryl-heteroaryl structural motif is frequently featured at the core of many natural products, pharmaceuticals, and electronic materials.[1] Carbon–carbon biheteroaryl linkages are generally considered formed through the C–C bond cross-coupling between a heteroarylhalide with a heteroaryl organometallic reagent.[2] However, the preactivation of heteroaromatic carbon fragments with metal-containing functionalities and halides could involve several synthetic steps. Moreover, several important types of heteroaryl organometallic compounds have proven to be inadequately stable to participate in cross-coupling reactions.[3–5] For example, the instability and difficult synthesis of 2-pyridyl organometallics severely limits their application.[6]. To solve this drawback, pyridine *N*-oxides have been introduced as widely available and bench-stable substrates for direct cross-coupling reactions.[7]

At present, C–H/C–H oxidative cross-coupling between two (hetero)arenes is regarded as one of the most attractive strategies for building biheteroaryl linkages without the need for the tedious prefunctionalization of starting materials.[8] However, this type of C–H/C–H cross-coupling for the unsymmetrical construction of "heteroaryl–heteroaryl" scaffolds has rarely been studied because of the daunting complexity in the inversion of reactivity and selectivity.[8] To the best of our knowledge, a few methods have been reported for the synthesis of the structure of 2-pyridinyl-1,2,3-triazoles because of their various biological activities.[9] However, the metal-catalyzed oxidative cross-coupling of two heteroaryl C-H bonds to form 1-benzyl-5-pyridinyl-1,2,3-triazole molecules remains a challenge. Moreover, only a few investigations of two heteroaryl C–H bonds forming 2-pyridinyl-thiophen(furan) have been reported to date; however, the substrates of pyridine *N*-oxides are limited only to 2-substituted pyridine *N*-oxides and quinoline *N*-oxides.[10] Additional, direct arylation of the 3-substituted pyridine *N*-oxides and isoquinoline *N*-oxide confronted the problem of regiochemistry because of a competition between C2 and C6 positions.[7j] With a continuing interest in C–H/C–H cross-coupling of Heterocyclic *N*-oxides[11] , we continued our efforts to expand the application and understanding of the metal-catalyzed cross-coupling between pyridine *N*-oxides and heterocycles. Herein, we illustrate an efficient and site-selective CH/CH cross-coupling of pyridine *N*-oxides with 1-benzyl-1,2,3-triazole, thiophen and furan derivatives.

We initially used the conditon similar to that reported[10a-b] for the oxidative CH/CH cross-coupling reaction of pyridine *N*-oxide (**1a**) and 1-(*p*-methoxylbenzyl)-1,2,3-triazoles (**2a**); however, the desired product (**3a)** was observed with low yield of 15%(Table 1, entry 1). From the tests using different oxidants, we found that the corresponding products were obtained with the incomplete ionization of silver salts (Ag_2CO_3, Ag_2O, and AgOAc). In addition, the oxidant Ag_2CO_3 was more effective than AgOAc, Ag_2O, Ag_2SO_4, $AgNO_3$, $Cu(OAc)_2$ H_2O, and $FeCl_3$ (Table 1, entries 2 to 7,) respectively. It was found that 2,6-lutidine[9c] produced a higher yield than pyridine and 1,10-phenanthroline as ligand (Table 1, entries 7 to 9,). Moreover, we found that the addition of DMSO with dioxane resulted in the highest yield of 83%(Table 1, entry 10) in comparison with other solvents, such as DMSO, DMF, and NMP (entries 10 to 15, respectively), even when the reaction was performed at 160 ℃

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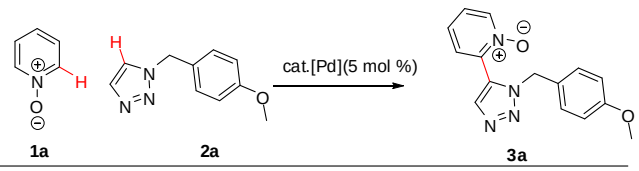
(Table 1, entry 16). The optimal yield can be achieved by using 5 mol % of $Pd(OAc)_2$, Ag_2CO_3 (2 equiv) , and 30 mol % of 2,6-lutidine and the desired product (**3a)** formed with complete regioselectivity (Table 1, entry 10). Moreover, no homocoupling product of **2a** was observed**.**

Table 1. Influence of reaction conditions on the reaction of 1a with 2a[a]



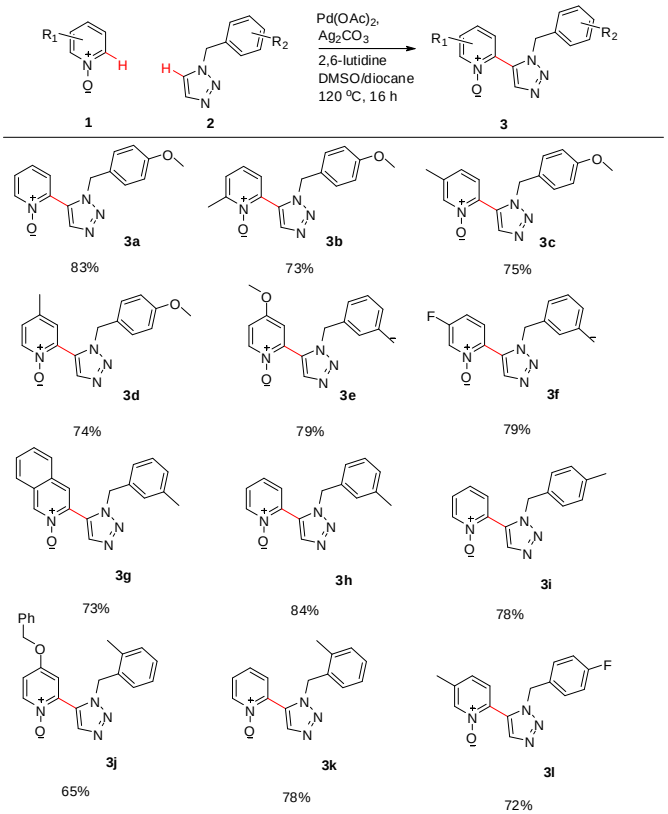
1a **2a** **3a**

entry	oxidant (2 equiv)	ligand	solvent	yield of **3a** (%)[c]
1	$Cu(OAc)_2$	pyridine	dioxane	15
2	$FeCl_3$	pyridine	dioxane	trace
3	Ag_2O	pyridine	dioxane	55
4	Ag_2SO_4	pyridine	dioxane	trace
5	$AgNO_3$	pyridine	dioxane	trace
6	AgOAc	pyridine	dioxane	46
7	Ag_2CO_3	pyridine	dioxane	53
8	Ag_2CO_3	Phen	dioxane	45
9	Ag_2CO_3	2,6-lutidine	dioxane	66
10	Ag_2CO_3	2,6-lutidine	5%DMSO/dioxane	83 (65)[b]
11	Ag_2CO_3	2,6-lutidine	10%DMSO/dioxane	51
12	Ag_2CO_3	2,6-lutidine	20%DMSO/dioxane	43
13	Ag_2CO_3	2,6-lutidine	DMSO	36
14	Ag_2CO_3	2,6-lutidine	DMF	43
15	Ag_2CO_3	2,6-lutidine	NMP	47
16	Ag_2CO_3	2,6-lutidine	NMP	trace

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), ligand (0.15 mmol) and oxidant (1.0 mmol) in 3 mL of solvent at 120 ℃ for 16 h. [b] no 2,6-lutidine was added. [c]Isolated yields

With the optimized conditions (Table 1, entry 10), We then tested the protocol for the cross-coupling of other pyridine *N*-oxides and 1-benzyl-1,2,3-triazoles(Table 2). As outlined, a wide range of various substituted pyridine *N*-oxides, thereby allowing a linkage of 2-methyl (**3b**), 3-methyl (**3c, 3l**), 4-methyl (**3d**), 4-methoxyl (**3e**), 4-benzyloxyl (**3j**), 3-fluoro(**3f**) gave the desired products in good yields. Furthermore, the above heteroarylation also reacts with other biologically important heteroarene cores, such as isoquinoline *N*-oxide, which only occurred at the C3 position with a yield of 73% (**3g**). No desired cross-coupling product was obtained when 4-nitropyridine and quinoline *N*-oxides were used as coupling partners. Notably, groups at the N-1 position of the triazole ring bearing *p*-methoxylbenzyl (**3a** to **3d**), *p*-tolylbenzyl (**3i**), *m*-tolyl- benzyl (**3e** to **3h**), *o*-tolylbenzyl (**3j** , **3k**) and *p*-fluorobenzyl (**3l**) can also be used for this reaction. Moreover, no reaction occurred under the same conditions if 1-phenyl-1,2,3-triazole reacts with pyridine *N*-oxide (**1a**).

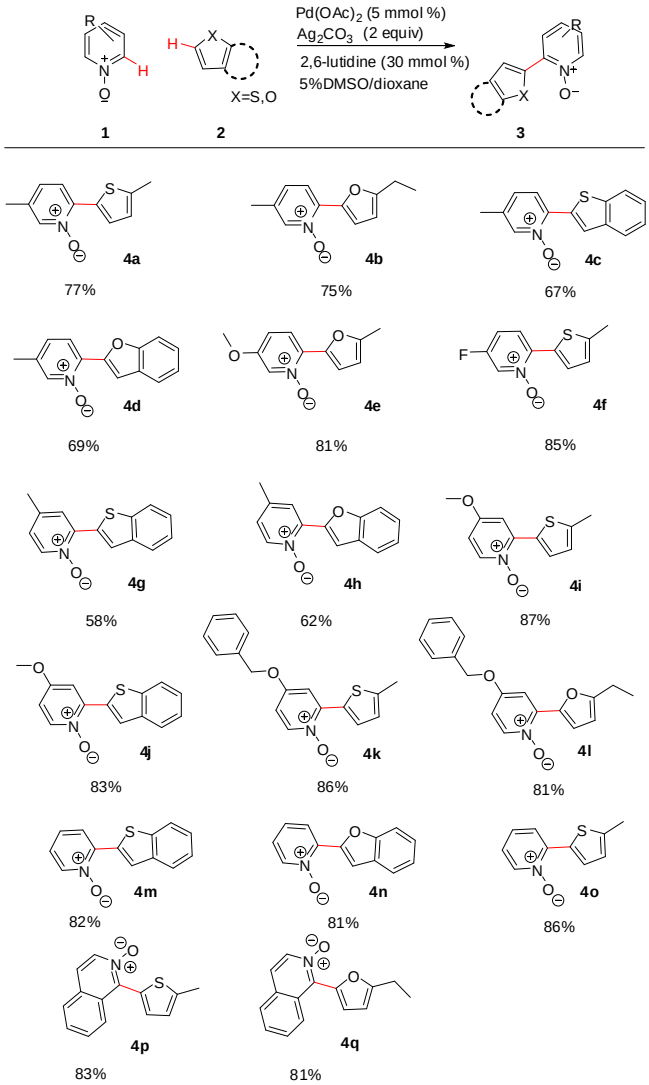
Table 2 . Scope of CH/CH cross-coupling of pyridine *N*-oxides with 1,2,3-trazoles[a,b]



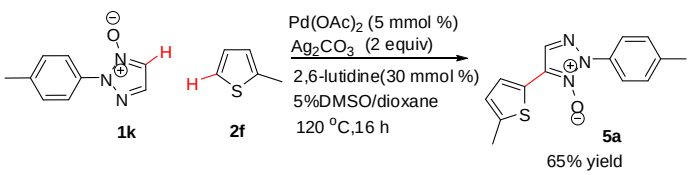
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), Ag_2CO_3 (1 mmol), and 2,6-lutidine (0.15 mmol) in 5%DMSO/1,4-dioxane (3 mL) at 120 ℃ for 16 h [b]Isolated yields

Using the above conditions, we also found that the cross-coupling reaction occurred when using thiophens and furans instead of 1-benzyl-1,2,3-triazoles as substrate. Then we explored the scope of the cross-coupling reactions of pyridine *N*-oxides with thiophens and furans (Table 3). Diverse decorated products **4a-4q** formed in moderate to good yields, and regioisomeric products were not observed. Notably, the high yields of product **4**, which originates from reaction of 3-substituted pyridine *N*-oxide with an electron-withdrawing group (**4f**) and 4-substituted pyridine *N*-oxide with an electron-donating group (**4e**, **4i** to **4l**), was obtained. Furthermore, thiophen and furan derivatives, namely, including 2-methylthiophen, 2-methylfuran, 2-ethylfuran, benzothiophen, and benzofuran can also be used for this reaction. The desired cross-coupling product was not obtained when 2-methylpyridine and 4-nitropyridine *N*-oxide were used as coupling partners. Surprisingly, the above heteroarylation also proceeded well with isoquinoline *N*-oxide (**4p**, **4q**), but the reaction only occurred at the C1 position of isoquinoline *N*-oxide in good yields. Notably, the desired product was not observed under the above conditions when quinoline *N*-oxide was used as substrate.

Table 3. Scope of CH/CH cross-coupling of pyridine *N*-oxides with thiophen or furan[a,b]



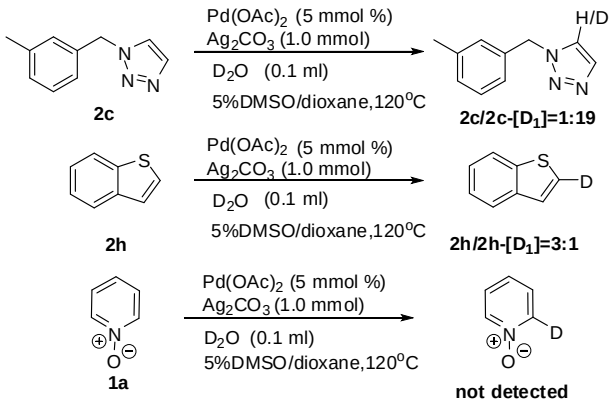
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), Ag_2CO_3 (1 mmol), and 2,6-lutidine (0.15 mmol) in 5%DMSO/1,4-dioxane (3 mL) at 120 ℃ for 16 h [b]Isolated yields



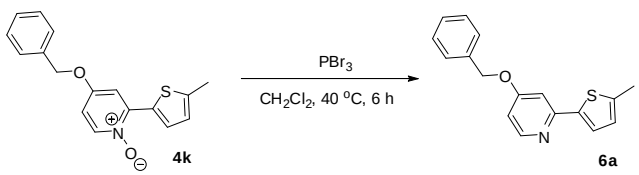
Scheme 1. C-H/C-H oxidative cross-coupling between 1,2,3-triazole *N*-oxides with 2-methylthiophen

Interestingly, under the same catalytic conditions, the cross-coupling product (**5a**) between 2-substituted 1,2,3-triazole *N*-oxides and 2-methylthiophen was formed with a moderate yield of 65% (Scheme 1).

To gain insight into the reaction mechanism, the H/D exchange control experiments for five-membered heterocyles **2c** and **2h** were performed. As shown in Scheme 2, moderate and high deuterium incorporation were observed respectively. Moreover, no deuterium incorporation occurred when pyridine *N*-oxide (**1a**) was applied to the above system (Scheme 2). The results indicated that the five-membered heterocycles should undergo a substitution reaction with Pd-catalyst to generate palladium intermediate. We proposed that the cross-coupling reaction should proceed through a plausible catalytic cycle similar to the typical mechanism of the cross-coupling reaction of pyridine *N*-oxide.[11a,12] Moreover, The results from the above experiments demonstrated that, relative to thiophens, this catalytic system inverted its high compatibility and reactivity in the cross-coupling reaction of 1-benzyl-1,2,3-triazole as substrates. Further studies are needed to understand the mechanism of the difference position cross-coupling of isoquinoline *N*-oxide with five-membered heterocycles.



Scheme 2. The H/D exchange control experiments



Scheme 3. Deoxygenation for biheterocyclic *N*-oxide

Lastly, heterocyclic *N*-oxide **3k** was easily reduced by PBr_3 to generate the corresponding biheterocycles **6a**, indicating that the cross-coupling reaction is practical for the preparation of biheteroaryl molecules (Scheme 3). Additionally, in contrast to these reported the protocol for direct arylation[7j] of the 3-substituted pyridine *N*-oxides and isoquinoline *N*-oxide, our catalytic system offers complete regioselectivity.

In summary, a highly efficient and regioselective oxidative cross-coupling for pyridine *N*-oxides with five-membered heterocycles through a two-fold C-H activation has been developed. Moreover, this catalytic system shows good compatibility with numerous synthetically relevant functional groups. We hope that this protocol

may provide insights into the synthesis of unsymmetrical biheteroaryl molecules in material and medical chemistry.

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