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Pd-Catalyzed Oxidative CH/CH Direct Coupling of Heterocyclic *N*-Oxides

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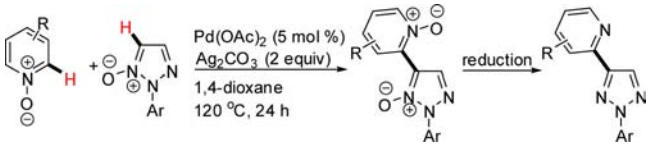
ABSTRACT



A highly efficient protocol for C−H/C−H cross-coupling has been found to occur between 2-aryl-1,2,3-triazole *N*-oxides and pyridine *N*-oxide derivatives. In addition, two homocoupling reactions of 2-substituted 1,2,3-triazole *N*-oxides and some pyridine *N*-oxide derivatives were developed. A possible pathway of C−H/C−H direct coupling is discussed.

Recently, transition-metal-catalyzed C−H bond activation for C−C bond formation has become a powerful tool for the construction of C−C bond frameworks.[1] Since 2005, pyridine and other heterocyclic *N*-oxides have been introduced as easily available and stable substrates for direct cross-coupling reactions by Fagnou and other groups. The scope of direct cross-coupling partners has broadened to include various (hetero) arene halides, arene boronic acid, alkenes, and even simple arenes such as benzene.[2]

Linked biheterocycles constitute an important class of heterocycles with numerous applications for various biologically active compounds and functional materials.[3] Considering their importance, the synthesis of biheterocycle units through transition-metal-catalyzed C−H bond activation has received increased attention. Transition-metal-catalyzed oxidative C−H/C−H cross-coupling between two (hetero) arenes is one of the most attractive approaches in forging biheteroaryl linkages, without the time-consuming and tedious prefunctionalization of both starting materials.[4] However, this type of C−H/C−H cross-coupling for the unsymmetrical construction of

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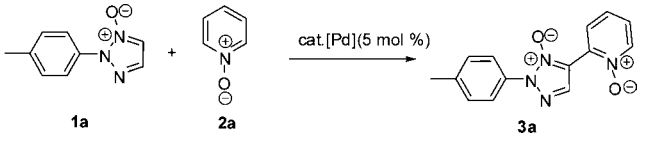
"heteroaryl–heteroaryl" scaffolds with double electron-deficient rings remains less explored because of a daunting hindrance in reactivity and selectivity inversion.[5] To our knowledge, a few methods have been reported for the synthesis of 2-pyridinyl-1,2,3-triazoles because of their various biological activities.[6] However, the metal-catalyzed oxidative cross-coupling of two heteroaryl C–H bonds to form 2-pyridinyl-1,2,3-triazole molecules remains a challenge. Furthermore, we have a continuing interest in the direct C5-functionalization of 2-substituted 1,2,3-triazole *N*-oxides.[2n] Thus, we propose that the introduction of the *N*-oxide moiety can increase the reactivity and selectivity of the oxidative C–H/C–H cross-coupling reaction. Herein, we illustrate an efficient site-selective CH/CH cross-coupling between 2-aryl-1,2,3-triazole *N*-oxides and other heterocyclic *N*-oxides, several of which are readily prepared in excellent yields or are commercially available. The resulting heterocyclic *N*,*N*-dioxides were efficiently reduced to the final products

Our study was instigated by an unexpected observation during the investigation of the Pd-catalyzed C–H functionalization reaction of 2-aryl-1,2,3-triazole *N*-oxides. During the tests with different cross-partners, we found that cross-coupling reactions occurred between 2-aryl-1,2,3-triazole *N*-oxides (**1a**) and pyridine *N*-oxide (**2a**) in a low yield of 28% (Table 1, entry 1). The oxidant, temperature, and solvent were found to play critical roles in the reaction efficiency. While no desired product was observed without the oxidant in the reaction system (entry 2), the oxidant Ag_2CO_3 was more effective than $Cu(OAc)_2 \cdot H_2O$, AgOAc, Ag_2O, Ag_2SO_4, and $AgNO_3$ (entries 3 to 7). The reaction proceeded highly efficiently when the reaction was performed at 120 °C (entries 7 to 9). We found that the use of 1,4-dioxane as solvent gave the highest yield (91%, entry 7) compared with other solvents, such as DMSO, toluene, and NMP (entries 10 to 12), even when the reaction was performed at 150 °C (entry 13). The optimal yield could be achieved by using 5 mol % of $Pd(OAc)_2$ and Ag_2CO_3 (2 equiv) in 1,4-dioxane, and the desired product **3a** formed with complete regioselectivity (entry 7).

With the optimized conditions (Table 1, entry 7), we then explored the scope of the cross-coupling reaction (Scheme 1). Similarly, the protocol was also applicable to various substituted pyridine *N*-oxides, thereby allowing an

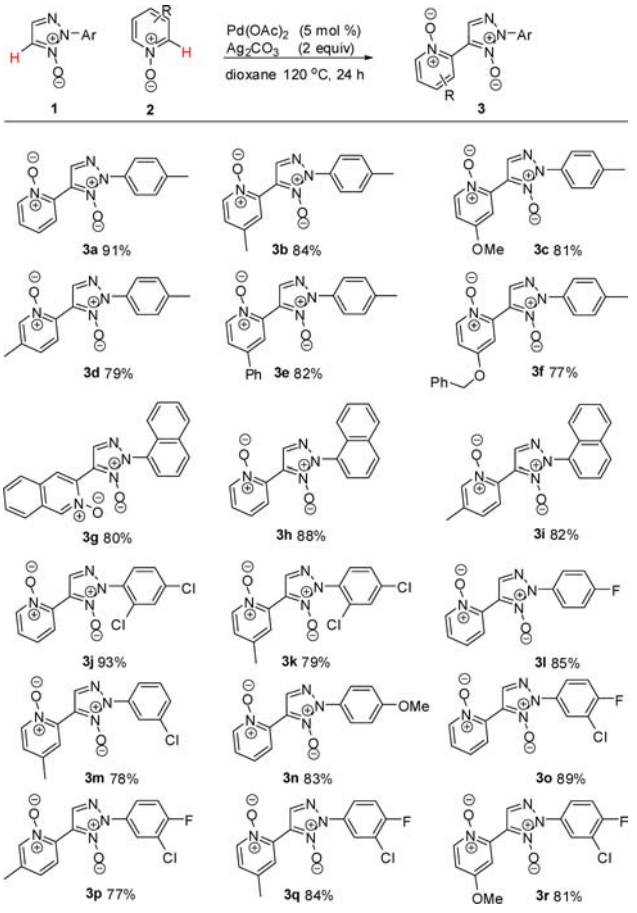
Table 1. Optimization of Typical Reaction Conditions[a]



entry	oxidant (2 equiv)	*t* (°C)	solvent	yield of **3a** (%)[c]
1	$Cu(OAc)_2$	120	dioxane	28
2	none	120	dioxane	trace
3	Ag_2O	120	dioxane	48
4	Ag_2SO_4	120	dioxane	13
5	$AgNO_3$	120	dioxane	8
6	AgOAc	120	dioxane	61
7	Ag_2CO_3	120	dioxane	91
8	Ag_2CO_3	60	dioxane	12
9[b]	Ag_2CO_3	90	dioxane	56
10	Ag_2CO_3	120	DMSO	67
11	Ag_2CO_3	120	Toluene	71
12	Ag_2CO_3	120	NMP	48
13	Ag_2CO_3	150	NMP	59

[a] Conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), and oxidant (1.25 mmol) in 1 mL of solvent for 24 h. [b] Run for 48 h. [c] Isolated yields.

Scheme 1. Substrate Scope[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), and Ag_2CO_3 (1 mmol) in 1,4-dioxane (1 mL) at 120 °C for 24 h. Isolated yields are shown.

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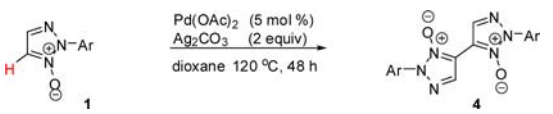
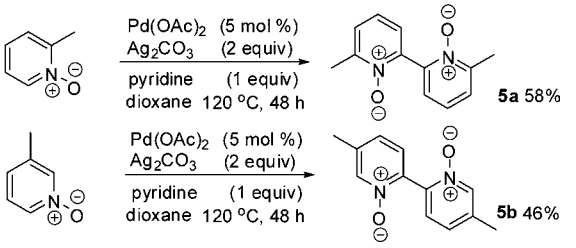
Table 2. Homocoupling of 2-Aryl-1,2,3-Triazole *N*-Oxides[a]



entry	*N*-oxides **1**	product **4**	yield of **4**(%)
1	**1a**	**4a**	30 (69)[b]
2	**1b**	**4b**	27 (74)[b]

[a] Conditions: **1** (0.5 mmol), **2** (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), and Ag_2CO_3 (1 mmol) in 1,4-dioxane (1 mL) at 120 °C for 48 h. [b] Pyridine (0.5 mmol) as base.

Scheme 2. Homocoupling of Pyridine *N*-Oxide Substrates



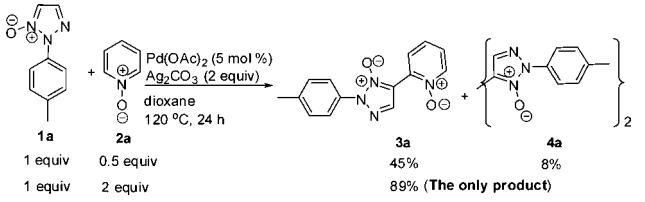
unprecedented direct linkage of 4-methyl (**3b**, **3k**, **3q**), 3-methyl (**3d**, **3i**, **3p**), 4-methoxyl (**3c**, **3r**), 4-phenyl (**3e**), and 4-benzyloxyl (**3f**) groups. Interestingly, the above heteroarylation also proceeded well with other biologically important heteroarene cores, such as isoquinoline *N*-oxide (**3g**), which only occurred at the C3 position. No desired cross-coupling product was obtained when 2-methylpyridine, 2-phenylpyridine, 4-nitropyridine, and quinoline *N*-oxides were used as coupling partners. Notably, aryl groups at the N-2 position of the triazole ring bearing *m*-tolyl (**3a** to **3f**), 1-naphthyl (**3g** to **3i**), 2,4- dichlorophenyl (**3j**, **3k**), 4-fluorophenyl (**3l**), 3-chlorophenyl (**3m**), 4-methoxylphenyl (**3n**), and the 3-chloro-4-fluorophenyl moiety (**3o** to **3r**) can also be used for this reaction. Such unsymmetrical biheterocyclic scaffolds are expected to possess important applications in medicinal and materials chemistry.

Interestingly, under the same catalytic conditions, the homocoupling product (**4a**, **4b**) of 2-substituted 1,2,3-triazole *N*-oxides formed in low yields, even with the extension of the reaction time to 48 h when the other coupling partners of the six-membered heterocycle *N*-oxide was free in the reaction system (Table 2). Notably, no reaction was observed when six-membered heterocycle *N*-oxides were applied to the above catalytic system instead of 2-substituted 1,2,3-triazole *N*-oxides.

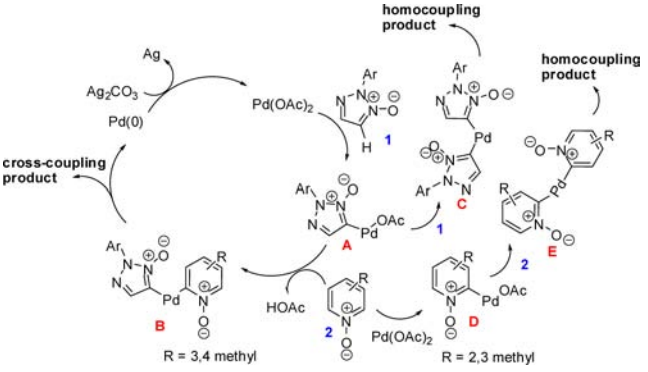
Considering that pyridine has been extensively used as a base or an activator in the oxidative CH/CH coupling of heteroarene *N*-oxides,[2f,n,5a] we speculated whether an additional introduction of pyridine added into this catalytic system could assist the C−H bond activation of heterocyclic *N*-oxides. As expected, the above reactions with up to 1 equiv of pyridine added significantly improved catalytic efficiency (Table 2). Surprisingly, **5a** and **5b** were obtained in low yields when 2-methylpyridine and 3-methylpyridine *N*-oxides, respectively, were applied to the catalytic system of $Pd(OAc)_2$, $AgCO_3$, and pyridine, and no reaction occurred when pyridine was free (Scheme 2). No homocoupling product was observed under the above conditions when pyridine, 4-methylpyridine, 4-nitropyridine, 2-phenylpyridine, quinoline, and isoquinoline *N*-oxides were used as substrates.

Further studies were conducted to determine the reaction mechanism. We performed the control experiment using a 2:1 mixture of **1a** and **2a** under the standard conditions. The reaction afforded **3a** in 45% yield and **4a** in 8% yield. Moreover, no homocoupling product of pyridine *N*-oxide was observed when the reaction was performed in an opposite ratio (Scheme 3). Therefore, 2-substituted 1,2,3-triazole *N*-oxides might be the preferred compound to undergo the C−H substitution of $Pd(OAc)_2$ for generating the palladium(II) intermediate.

Scheme 3. Control Experiment



Scheme 4. Plausible Catalytic Cycle



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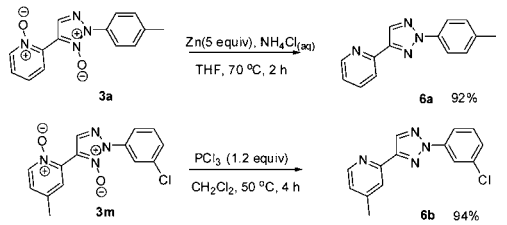
Scheme 5. Deoxygenation for Biheterocyclic *N*,*N*-Dioxides



Although more detailed investigations on the reaction mechanism are currently underway,[5a,7] we propose that the Pd-catalyzed direct coupling proceeds through a plausible catalytic cycle (Scheme 4). In the first step, the above observations indicated that the abstraction of hydrogen from the 2-substituted 1,2,3-triazole *N*-oxides easily occurs in the reaction system. Thus, the 2-substituted 1,2,3-triazole *N*-oxides would undergo regioselective electrophilic C−H substitution (S_EAr) of Pd $(OAc)_2$ to generate the palladium(II) intermediate (**A**). In the second step, bisheteroarylpalladium species (**B**) is formed by C−H substitution of the intermediate **A** with pyridine *N*-oxide. Compared with the intermediate **B** related to the cross-coupling, the homocoupling intermediate (**C**) might form with some difficulty because of its lower relative rate than that of **B**. Therefore, when a catalyst, 2-substituted 1,2,3-triazole *N*-oxide, and pyridine *N*-oxide coexist in a reaction system, **B** might be the predominant intermediate after the formation of **A**. The homocoupling of the 2-substituted 1,2,3-triazole *N*-oxides proceeded through the formation of intermediate **C** when *N*-oxide **2** was free in the reaction system. The introduction of pyridine should give more reaction activity and an increased rate to form intermediate **C**. The result demonstrated that the catalytic system inverted its selectivity in the homocoupling reaction of the six-membered heterocycle *N*-oxides. Further studies are needed to understand the mechanism of the homocoupling of six-membered heterocycle *N*-oxides in a Pd-catalyzed C−H functionalization reaction.

Finally, **3a** and **3m** were easily reduced by Zn[8] or PCl_3[2,9] to produce the corresponding biheterocycles, showing that the new CH/CH cross-coupling reaction is practical for the preparation of unsymmetrical and symmetrical biheteroaryl molecules (Scheme 5).

In summary, for the first time, we have developed a highly efficient and regioselective oxidative cross-coupling and homocoupling among 2-substituted 1,2,3-triazole *N*-oxides, pyridine *N*-oxide derivatives, and even isoquinoline *N*-oxide through a 2-fold C−H activation. This protocol constitutes a rather rare example of synthesis of unsymmetrical and symmetrical biheterocyclic *N*,*N*-dioxides and the corresponding biheterocycles. In addition, this protocol shows good compatibility with numerous synthetically relevant functional groups, thus providing a novel practical tool for the preparation of unsymmetrical and symmetrical biheterocyclic *N*,*N*-dioxides. We hope that this investigation may have a broader impact on the synthesis of unsymmetrical and symmetrical biheterocyclic *N*,*N*-dioxides and biheteroaryl molecules in material, medical, and natural product chemistry.

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Supporting Information Available. Typical experimental procedures, characterization data, and ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.