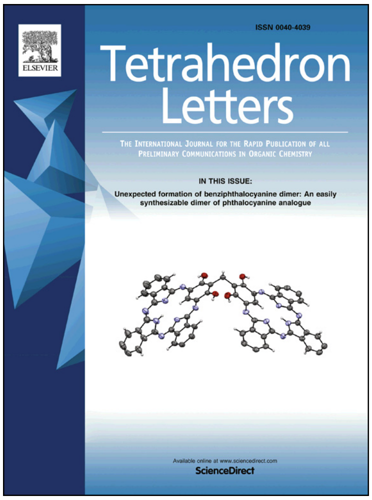

Room-Temperature Oxidative Suzuki Coupling Reaction of 1,2,3-Triazole *N*-Oxides

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Room-Temperature Oxidative Suzuki Coupling Reaction of 1,2,3-Triazole *N*-Oxides

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ABSTRACT

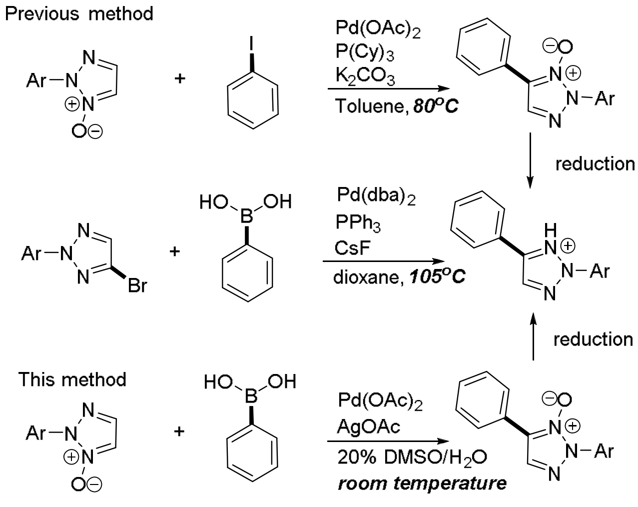
This study develops a new efficient pathway for synthesis of 2,4-disubstituted 1,2,3-triazoles through regioselective direct arylation between 2-aryl-1,2,3-triazole *N*-oxides and Ar-B$(OH)_2$. The reaction proceeds smoothly at room temperature and exhibits good yield and high C5 position selectivity. The possible pathway of oxidative Suzuki coupling is also discussed. This simple methodology can be used to construct 2,4-disubstituted 1,2,3-triazole moiety.

Introduction

1,2,3-Triazoles, which exhibit unique chemical and structural properties, are an important class of heterocycles with numerous applications in materials and medicinal chemistry.[1–4] Considering the rapidly increasing number of requirements for synthesis of these heterocycles, scholars must develop effective methods for preparation of diverse 1,2,3-triazole derivatives.[5–8] Various protocols involving coupling with 1,2,3-triazole derivatives have been established.[9–11]

C–H bond activation reactions have gained increasing attention from academic and industrial chemists[12–14] because these reactions can shorten the synthesis route and allow the utilization of affordable and readily available starting materials. The Pd-catalyzed direct cross coupling of arenes and arylboronic acid, also called oxidative Suzuki-type reaction, is a representative of C–H bond activation reactions. Previous studies reported that these reactions require elevated temperatures,[15,16,18] which severely limit the compatibility of the substrates and their large-scale applications. Thus, identifying mild reaction conditions that can proceed at ambient temperature is necessary to broaden the applicability of these transformations (Scheme 1).[15,18]

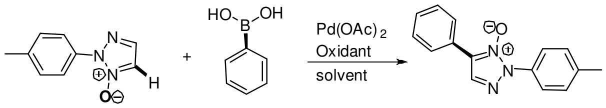
Focusing on the direct arylation of 1,2,3-triazole *N*-oxides,[17–19] we aim to expand the reaction at room temperature for the formation of 2,4-bisaryl 1,2,3-triazoles.



Scheme 1. Strategy for preparing 2,4-bisaryl 1,2,3-triazoles by C–H activation.

To our knowledge, most direct arylation methods of 1,2,3-triazole rings are mainly limited to 1-substituted 1,2,3-triazole derivatives; moreover, the direct arylation of 2-substituted 1,2,3-triazoles has been rarely investigated due to their complex reactivity and selectivity[20]. In this study, we report an efficient method for synthesis of 2,4-disubstituted 1,2,3-triazoles through direct arylation between arylboronic acid and 2-aryl-1,2,3-

Table 1. Screening for optimal reaction conditions[a]



1a 2a 3a

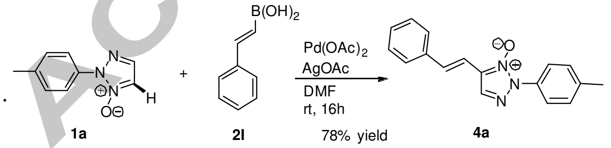
Entry	Oxidant(1.3equiv)	Temperature	solvent	Yield of 3a (%)^b
1	Ag_2CO_3	25°C	Dioxane	35%
2	AgOAc	25°C	Dioxane	56%
3	Ag_2O	25°C	Dioxane	8%
4	$AgNO_3$	25°C	Dioxane	trace
5	Ag_2SO_4	25°C	Dioxane	trace
6	$CuSO_4$	25°C	Dioxane	trace
7	AgOAc	25°C	Dioxane	77%
8	AgOAc	25°C	DMF	87%
9	AgOAc	25°C	DMSO	70%
10	AgOAc	25°C	Toluene	22%
11^c	AgOAc	70°C	DMF	23%
12^c	AgOAc	100°C	DMF	trace
13	none	25°C	DMF	trace

[a] Conditions: 1 (0.50 mmol), 2a (0.60 mmol), Pd(OAc)$_2$ (5.0 mol%), Oxidant (5.0 mol%), solvent (2.0 ml), rt, and 16 h, under air. [b] Yield of isolated product. [c] Biphenyl was obtained.

triazole *N*-oxides at room temperature, many of which were obtained in good yields.

Results and Discussion

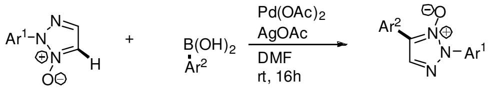
Basing on the results of published methods for the typical reaction conditions for direct arylation,[7] we tested the reaction of 2-(p-tolyl)-1,2,3-triazole *N*-oxide (1a) and phenylboronic acid at room temperature (Table 1). AgOAc was more effective than Ag_2CO_3, Ag_2O, Ag_2SO_4, $AgNO_3$, and $CuSO_4$ (entries 1–7). Moreover, DMF was more effective than 1,4-dioxane, DMSO, and toluene as solvent (entries 7–10). Although the desired conditions for 2-substituted 1,2,3-triazole *N*-oxide arylation provided the direct product 3a in 87% isolated yield at room temperature (entry 7), we investigated whether the reaction might be performed at high temperatures (entries 4–6). Notably, only 23% product yield was obtained, and 45% biphenyl yield was detected at 70 °C (entry 11). No desired product was obtained, and 95% biphenyl yield was observed when the temperature was changed to 100 °C (entry 12).



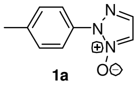
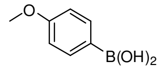
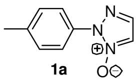
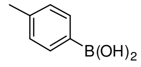
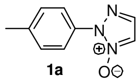
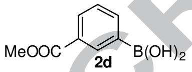
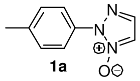
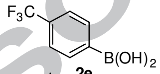
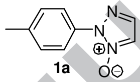
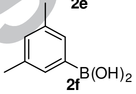
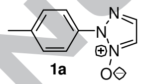
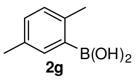
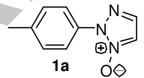
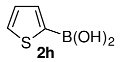
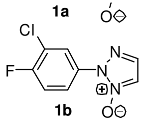
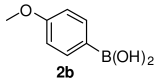
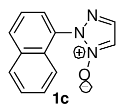
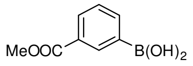
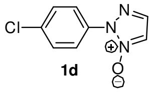
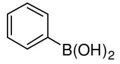
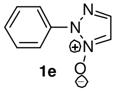
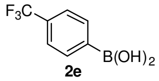
1a 2l 4a

Scheme 2. Reaction between (***E***)-styreneboronic acid and **1a**.

Table 2. C-5 arylation of 2-aryl-1,2,3-triazole N-oxides[a].



1 2 3

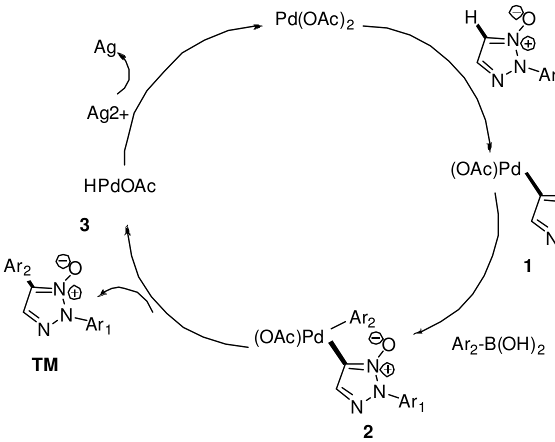
Entry	1	2	3	Yield of 3 (%)^b
1	 1a	 2b	3b	84%
2	 1a	 2c	3c	87%
3	 1a	 2d	3d	81%
4	 1a	 2e	3e	78%
5	 1a	 2f	3f	89%
6	 1a	 2g	3g	64%
7	 1a	 2h	3h	85%
8	 1b	 2b	3i	83%
9	 1c	 2d	3j	80%
10	 1d	 2a	3k	88%
11	 1e	 2e	3l	79%

[a] Conditions: 1 (0.50 mmol), 2a (0.60 mmol), Pd(OAc)$_2$ (5.0 mol%), AgOAc (1.0 mmol), DMF (2.0 ml), rt, and 16 h. [b] Yield of the isolated product.

Under the optimized conditions, we tested the scope of the reaction of 2-aryl-1,2,3-triazole *N*-oxides **1** and arylboronic acids **2** (Table 2). Diverse decorated products **3b–l** were formed, with good to excellent yields. Both electron-rich (entries 1, 2, 5, 6, and 8) and electron poor (entries 3 and 4) arylboronic acids were compatible. Thiopheneboronic acids were also applied to this system (entries 7). Notably, aryl groups at the *N*-2 position of the triazole ring bearing *m*-tolyl (entries 1–7), phenyl (entries 11), 1-naphthyl (entries 9), 4-chloro-phenyl (entry 10), and the 3-chloro-4-fluoro-phenyl (entry 8) moiety can be used for the reaction. Moreover, (***E***)-styreneboronic acid 2i can be used for this reaction with 2-aryl-1,2,3-triazole *N*-oxides **1a**. The product **4a** was formed in moderate yield (Scheme 2).

In this study, we propose a Pd-catalyzed direct arylation that proceeds through a pathway similar to the typical mechanism of direct arylation between pyridine *N*-oxides and arylboronic acids (Scheme 3).[21,22] We performed a control experiment using phenylboronic acid and iodobenzene or bromobenzene as coupling partner under standard conditions. No desired product was observed, indicating that the activity of C–H bond on the C-5 position in 2-aryl-1,2,3-triazole *N*-oxides should be higher than the C–Br or C–I bond on aryl halides under this condition. Further studies must be performed to elucidate the mechanism of the oxidative Suzuki coupling of 1,2,3-triazole *N*-oxides with arylboronic acids at room temperature.

The deoxygenation of the arylated *N*-oxides to the desired 1,2,3-triazoles can be conveniently achieved with high yields through the Pd-catalyzed reduction with ammonium formate or PBr_3.[19,23] Although few scholars have developed the synthesis of 2,4-disubstituted 1,2,3-triazoles,[24] this protocol can provide a valuable alternative for synthesis of 2,4-disubstituted 1,2,3-triazoles.



Scheme 3. Possible pathway for oxidative Suzuki coupling.

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Conclusion

We reported an efficient direct coupling reaction between 2-aryl-1,2,3-triazole *N*-oxides and arylboronic acids at room temperature for synthesis of 2,4-disubstituted 1,2,3-triazoles. The protocol can be applied to obtain moderate yields of styreneboronic acid and 1,2,3-triazole *N*-oxides. The proposed method can be used as an alternative to existing procedures for synthesis of 2,4-disubstituted 1,2,3-triazoles in organic chemistry and medical chemistry.

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Supplementary data

Supplementary data (Experimental details, ^1H NMR data and spectra, ^{13}C NMR data and spectra, FT-IR data and spectra) associated with this article can be found, in the online version, at http://dx.doi.org/000000.

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Graphical Abstract

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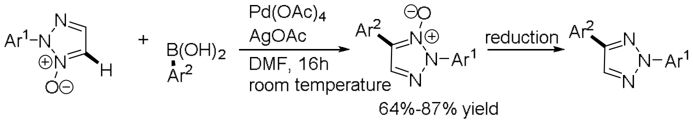
Wei Liu, Yan-Yan Yu, Bo-Yi Fan and Chun-Xiang Kuang



This study develops a new efficient pathway for synthesis of 2,4-disubstituted 1,2,3-triazoles through regioselective direct arylation between 2-aryl-1,2,3-triazole *N*-oxides and Ar-$B(OH)_2$. The reaction proceeds smoothly at room temperature and exhibits good yield and high C5 position selectivity. The possible pathway of oxidative Suzuki coupling is also discussed. This simple methodology can be used

Highlight

1）A new efficient method for synthesis of 2,4-disubstituted 1,2,3-triazoles through oxidative Suzuki reaction is developed.

2）The reaction can be carried out smoothly at room temperature with good yield.

3）The possible mechanism of the oxidative Suzuki reaction is discussed.