Palladium-catalyzed highly regioselective oxidative homocoupling of 1,2,3-triazole *N*-oxides

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ABSTRACT

A convenient and highly regioselective palladium-catalyzed direct C–H homocoupling of 1,2,3-triazole *N*-oxides was developed in the presence of silver carbonate and 1,10-phenanthroline. This protocol provides a straightforward and operationally simple route for the preparation of bis(1,2,3-triazole)3,3′-dioxides in good to excellent yields.

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Introduction

1,2,3-Triazoles are important heterocycles,[1] which are widely used in pharmaceuticals and agrochemicals. 1,2,3-Triazoles have been shown to exhibit a wide spectrum of biological activities,[2] such as antibacterial, herbicidal, fungicidal, antiallergic, and anti-HIV properties. For example, 4-aryl-1*H*-1,2,3-triazoles have been used as human methionine aminopeptidase (hMetAP2) and indoleamine 2,3-dioxygenase (IDO) inhibitors, and are expected to become medicines to treat cancers, AIDS, Alzheimer's disease, tristimania, cataracts, and some other serious diseases.[3] In addition, 1,2,3-triazoles have attracted increasing attention as an important class of heterocycles with numerous applications in materials and synthetical chemistry.[4,5] Since 2005, the pyridine, azine, diazine, azole, 1,2,3-triazole, and other heterocyclic *N*-oxides have been introduced as easily available and stable substrates for direct cross-coupling reactions by Fagnou[6] and other groups.[7] Recently, our group has developed efficient direct C5-amination, thiolation, and arylation of 1,2,3-triazole *N*-oxides.[8]

Linked biheterocycles are important as fine chemicals and constitute an important class of heterocycles with numerous applications for various biologically active compounds and functional materials.[9] Considering their importance, developing efficient synthetic methods for the formation of carbon–carbon bonds to prepare biheteroaryls is a worthwhile task in organic synthesis. Over the past years, the direct dehydrogenative coupling through the cleavage of two C–H bonds for the synthesis of biheteroaryls has attracted considerable attention in modern organic synthesis due to its synthetic efficiency and atom economy.[10] Although those elegant reactions have been developed, there is still an intrinsic need to develop biheterocycle *N*-oxides. Herein, we report an efficient palladium-catalyzed highly regioselective oxidative homocoupling of 1,2,3-triazole *N*-oxides to construct bitriazole *N*-oxides. To our knowledge, the metal-catalyzed oxidative homocoupling of two *N*-oxide C–H bonds to form biheteroaryl *N*-oxides still remained elusive.[5b]

To begin our investigation, 2-phenyl-2*H*-1,2,3-triazole 1-oxide (**1a**) was selected as a model system to screen the optimal conditions, and the results are summarized in Table 1. First, with the combination of Pd(OAc)$_2$ (5 mol%), Ag$_2$CO$_3$ (1 equiv), PPh$_3$ (0.2 equiv), and K$_3$PO$_4$ (1 equiv) in DMF at 100 °C for 24 h, the desired homocoupling product **2a** was obtained in 36% isolated yield (Table 1, entry 5). Other transition metal catalysts, such as Cu(OAc)$_2$, FeCl$_3$, AgNO$_3$, and NiSO$_4$, showed inferior or no reactivities (Table 1, entries 1–4). Among the examination of palladium catalysts, other palladium catalysts, including PdCl$_2$, Pd(PPh$_3$)$_4$, and Pd/C, were inferior to Pd(OAc)$_2$ (Table 1, entries 5–8). No desired product was observed in a control experiment without the addition of Pd catalyst (Table 1, entry 9). Among the oxidants we tested, Ag$_2$CO$_3$ was shown to be the most effective one, while other oxidants such as AgOAc, AgNO$_3$, AgBF$_4$, and AgNO$_2$ proved to be less effective (Table 1, entries 10–13). Subsequently, different bases were examined, including Na$_2$CO$_3$, Cs$_2$CO$_3$, LiOH, and *t*-BuOK.

Table 1
Selected optimization of the reaction conditions[a]
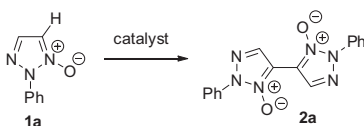
Entry	Catalyst	Base	Ligand	Solvent	Yield[b] (%)
1	Cu(OAc)$_2$	K$_3$PO$_4$	PPh$_3$	DMF	7
2	FeCl$_3$	K$_3$PO$_4$	PPh$_3$	DMF	0
3	Ag$_2$CO$_3$	K$_3$PO$_4$	PPh$_3$	DMF	0
4	NiSO$_4$	K$_3$PO$_4$	PPh$_3$	DMF	0
5	Pd(OAc)$_2$/Ag$_2$CO$_3$	K$_3$PO$_4$	PPh$_3$	DMF	36
6	PdCl$_2$/Ag$_2$CO$_3$	K$_3$PO$_4$	PPh$_3$	DMF	20
7	Pd(PPh$_3$)$_4$/Ag$_2$CO$_3$	K$_3$PO$_4$	PPh$_3$	DMF	17
8	Pd/C/Ag$_2$CO$_3$	K$_3$PO$_4$	PPh$_3$	DMF	10
9	—	K$_3$PO$_4$	PPh$_3$	DMF	0
10	Pd(OAc)$_2$/AgOAc	K$_3$PO$_4$	PPh$_3$	DMF	25
11	Pd(OAc)$_2$/AgNO$_3$	K$_3$PO$_4$	PPh$_3$	DMF	21
12	Pd(OAc)$_2$/AgBF$_4$	K$_3$PO$_4$	PPh$_3$	DMF	19
13	Pd(OAc)$_2$/AgNO$_2$	K$_3$PO$_4$	PPh$_3$	DMF	15
14	Pd(OAc)$_2$/Ag$_2$CO$_3$	K$_2$CO$_3$	PPh$_3$	DMF	35
15	Pd(OAc)$_2$/Ag$_2$CO$_3$	Cs$_2$CO$_3$	PPh$_3$	DMF	47
16	Pd(OAc)$_2$/Ag$_2$CO$_3$	LiOH	PPh$_3$	DMF	52
17	Pd(OAc)$_2$/Ag$_2$CO$_3$	t-BuOK	PPh$_3$	DMF	76
18	Pd(OAc)$_2$/Ag$_2$CO$_3$	t-BuOK	1,10-Phen	DMF	85[c]
19	Pd(OAc)$_2$/Ag$_2$CO$_3$	t-BuOK	4,4-bipy	DMF	43[c]
20	Pd(OAc)$_2$/Ag$_2$CO$_3$	t-BuOK	—	DMF	20[c]
21	Pd(OAc)$_2$/Ag$_2$CO$_3$	t-BuOK	1,10-Phen	t-BuOH	48[c]
22	Pd(OAc)$_2$/Ag$_2$CO$_3$	t-BuOK	1,10-Phen	1,4-dioxane	52[c]
23	Pd(OAc)$_2$/Ag$_2$CO$_3$	t-BuOK	1,10-Phen	toluene	31[c]

[a] Conditions: **1a** (0.2 mmol), catalyst (0.01 mmol), additive (0.2 mmol), ligand (0.04 mmol), base (0.2 mmol), and solvent (1 mL), 100 °C, 24 h, under argon.
[b] Isolated yield.
[c] Under open air.

A significant improvement in yield was observed when t-BuOK was used as a base. In this instance, product **2a** was isolated in 76% yield (Table 1, entry 17).

Additionally, the influence of the ligand on the reaction efficiency was also noteworthy. When 1,10-phenanthroline, 4,4′-bipyridine were used as the ligand, **2a** was obtained in 85% and 43% yields, respectively (Table 1, entries 18–19). In the absence of ligand, the reaction gave the product **2a** in a poor yield of 20% (Table 1, entry 20). Finally, the effect of solvents was examined. Disappointingly, a lower yield of **2a** was obtained when other commonly used solvents such as t-BuOH, 1.4-dioxane, and toluene were employed (Table 1, entries 21–23). On the basis of our screening experiments, the best results were obtained using a treatment of 5 mol% Pd(OAc)$_2$, 1 equiv of Ag$_2$CO$_3$, 20 mol% 1,10-phenanthroline, 1 equiv of t-BuOK in DMF at 100 °C for 24 h, which afforded the desired product **2a** in high yield (85%, entry 18).

To further explore the generality and scope of this palladium-catalyzed oxidative homocoupling reaction, a variety of substituted 1,2,3-triazole N-oxides was examined for the synthesis of biheteroaryl N-oxide **2**. In general, the reaction proceeded smoothly to give the desired products **2** in good to excellent yields. The electronic nature of the aryl groups at the N-2 position of the triazole ring did not play a key role. Both electron-rich and electron-poor 2-substituted 1,2,3-triazole N-oxides were good substrates. Substitutions at the C-2, C-3, and C-4 of position of the phenyl ring were all well tolerated. However, electron-poor triazole substrates bearing aryl groups at the N-2 position of the triazole ring furnished products with better yields compared with electron-rich counterpart. For example, the 3-chloro substituted substrate gave its product in higher yields than 3-methyl substituted substrate (Table 2, entries 3 and 10). To our delight, the reaction showed good compatibility with many valuable functional groups such as fluoro, chloro, trifluoromethyl, methyl, and

Table 2
Substrate scope[a]
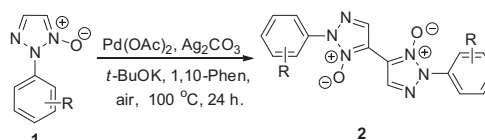
Entry	R	Product	Yield[b]
1	H	**2a**	85
2	4-Me	**2b**	83
3	3-Me	**2c**	77
4	2-Me	**2d**	68
5	2,5-Me$_2$	**2e**	79
6	3,4-Me$_2$	**2f**	80
7	4-OMe	**2g**	63[c]
8	2-F	**2h**	86
9	4-F	**2i**	88
10	3-Cl	**2j**	93
11	4-CF$_3$	**2k**	90
12	2,4-Cl$_2$	**2l**	86

[a] Conditions: **1** (0.2 mmol), Pd(OAc)$_2$ (0.01 mmol), Ag$_2$CO$_3$ (0.2 mmol), 1,10-phen (0.04 mmol), t-BuOK (0.2 mmol), and DMF (1 mL), 100 °C, 24 h., under open air.
[b] Isolated yields.
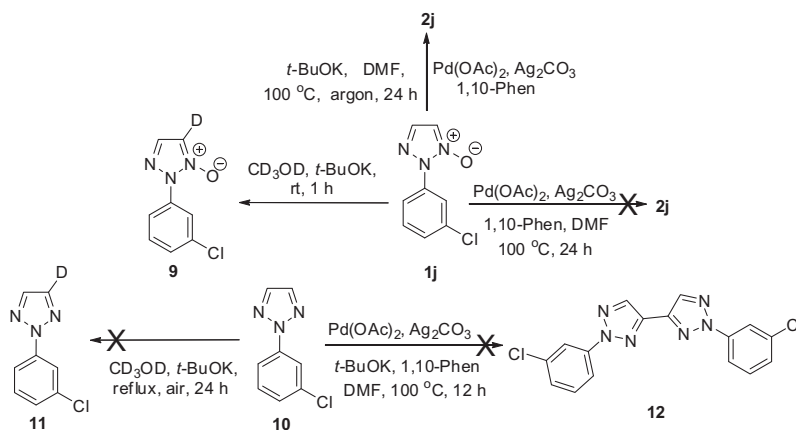[c] 2-(4-Hydroxylphenyl)-2′-(4-me-thoxyphenyl)-2H,2′H-(4,4′-bi(1,2,3-triazole)) 3,3′-dioxide was obtained.

methoxyl. Tolerance to the fluoro and chloro functional groups is especially noteworthy since they are useful for subsequent cross-coupling reactions. Interestingly, when 2-(4-methoxyphenyl)-2H-1,2,3-triazole 1-oxide was subjected to the standard reaction conditions, and demethyl cross-coupling product **2g** was obtained in 63% yield (Table 2, entry 7).
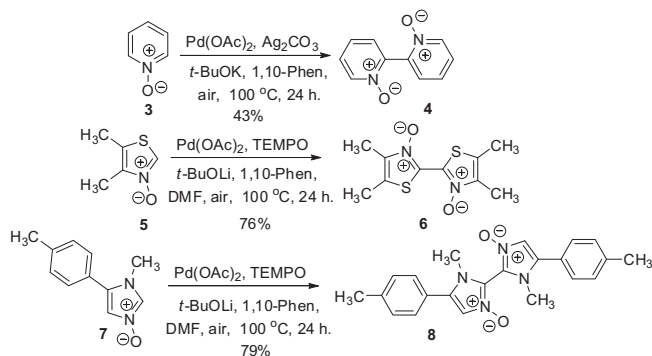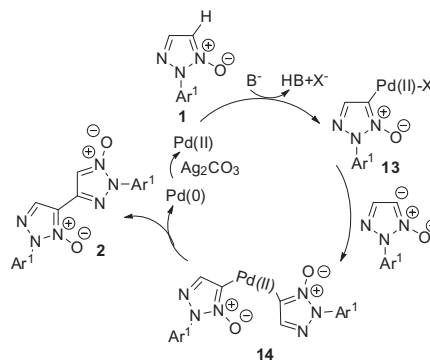
Scheme 1. Homocoupling of other heterocyclic N–O oxides.

Scheme 3. Plausible catalytic cycle of oxidative homocoupling of 1,2,3-triazole *N*-oxides.

With the promising results for bis(1,2,3-triazole)3,3′-dioxides formation, we further explored the possibility of extending the reaction to the more challenging other heterocyclic N–O oxides, which were not accessible under the standard reaction conditions. Gratifyingly, when TEMPO was used as the oxidant instead of Ag$_2$CO$_3$, the homocoupling reaction worked well with 4,5-dimethylthiazole 3-oxide **5** and 1-methyl-5-(*p*-tolyl)-1*H*-imidazole 3-oxide **7**, providing corresponding products in good yields (Scheme 1).

To obtain some mechanistic insights for this transformation, the following experiments were carried out (Scheme 2). Firstly, the rate of deuterium incorporation at C5 on the triazole *N*-oxide ring is more than 95%, indicating that the deuterium exchange between **1j** and CD$_3$OD would proceed quickly in the presence of *t*-BuOK, giving the deuterated product **9**. In contrast, the H/D exchange at C4 of **10** with CD$_3$OD under basic reaction conditions (*t*-BuOK, CD$_3$OD, reflux) afforded only the starting materials. This result indicated that H/D exchange at C4 of **10** did not occur under our reaction conditions. Secondly, the reaction of 1,2,3-triazole *N*-oxide **1j** was performed in the absence of *t*-BuOK, and no corresponding homocoupling product was detected. These results indicated that the 5-position of 1,2,3-triazole *N*-oxide **1j** is more electron-deficient and Pd-catalyzed C–C bond formation is initiated by cleavage of the C-5–H. Thirdly, the homocoupling of **1j** under an argon atmosphere (in the absence of molecular oxygen) furnished affording the corresponding dimer **2j** in 87% yield, indicating that molecular oxygen is not crucial for the reaction. Fourthly, when **10** were subjected to the standard reaction conditions, no reaction was observed. This result further indicated that the homocoupling formation is initiated by cleavage of the C-5–H.

Therefore, on the basis of the previous literature[5,11] and the above observations, a plausible mechanism to realize the oxidative homocoupling of 1,2,3-triazole *N*-oxides is shown in Scheme 3. First, the Pd(II) catalyst reacts with the deprotonated 1,2,3-triazole *N*-oxide **1** in the C-5 position to form an intermediate **13**, which is subsequently displaced by another deprotonated 1,2,3-triazole *N*-oxide to form intermediate **14**. Finally, a reductive elimination of **14** affords the final product **2** and the Pd(0) catalyst is reoxidized to Pd(II) by Ag$_2$CO$_3$, thus closing the catalytic cycle.

Conclusions

In conclusion, we have described a convenient C–H homocoupling of 1,2,3-triazole *N*-oxides with excellent C-3 regioselectivity. This reaction provides a new avenue for developing C–C bond formation to synthesize bis(1,2,3-triazole)3,3′-dioxides under mild conditions.[12] Moreover, it has several advantages: (1) the operational simplicity makes it potentially useful, (2) it is highly regioselective (5,5′-linkage), (3) the high halogen compatibility of the process, (4) this homocoupling reaction proceeds without exclusion of moisture or air from the reaction mixture and allows the isolation of the desired bis(1,2,3-triazole)3,3′-dioxides in good to excellent yields.[13]

Acknowledgments

Scheme 2. Control experiments for investigation of the mechanism.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.032.

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12. ***General Procedure for the Preparation of 2***: To a solution of 2-aryl-1,2,3-triazole *N*-oxide (0.2 mmol), Pd(OAc)$_2$ (0.01 mmol), Ag$_2$CO$_3$ (0.2 mmol), and 1,10-phen (0.04 mmol) in DMF (1 mL) was added *t*-BuOK (0.2 mmol) under an air atmosphere and the mixture was stirred at 100 °C for 24 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1:2) to yield the corresponding product **2**.

13. *General procedure for the preparation of **6** and **8***: To a solution of 4,5-dimethylthiazole 3-oxide or 1-methyl-5-(*p*-tolyl)-1*H*-imidazole 3-oxide (0.2 mmol), Pd(OAc)$_2$ (0.01 mmol), TEMPO (0.2 mmol), and 1,10-phen (0.04 mmol) in DMF (1 mL) was added *t*-BuOLi (0.2 mmol) under an air atmosphere and the mixture was stirred at 100 °C for 24 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: CH$_2$Cl$_2$/CH$_3$OH = 10:1) to yield the corresponding product **6** or **8**.