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C–N Bond Formation

The Development of Copper-Catalyzed Aerobic Oxidative Coupling of H-Tetrazoles with Boronic Acids and an Insight into the Reaction Mechanism

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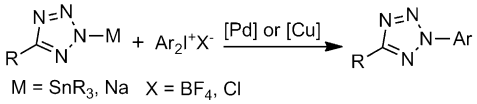
Abstract: The development of a highly efficient and practical protocol for the direct C–N coupling of H-tetrazole and boronic acid was presented. A careful and patient optimization of a variety of reaction parameters revealed that this conventionally challenge reaction could indeed proceed efficiently in a very simple system, that is, just by stirring the tetrazoles and boronic acids under oxygen in the presence of different Cu^{I} or Cu^{II} salts with only 5 mol% loading in DMSO at 100 °C. Most significantly, the reaction could proceed very smoothly in a regiospecific manner to afford the 2,5-disubstituted tetrazoles in high to excellent yields. A mechanistic study revealed that both tetrazole and DMSO are crucial for the generation of catalytically active copper species in the reaction process in addition to their role as reactant and solvent, respectively. It is demonstrated that in the reaction cycle, the Cu^{I} catalyst could be oxidized to Cu^{II} by oxygen to form a $[CuT_2D]$ complex (T = tetrazole anion; D = DMSO) through an oxidative copper amination reaction. The Cu^{II} complex thus formed was confirmed to be the real catalytically active copper species. Namely, the Cu^{II} complex disproportionates to aryl Cu^{III} and Cu^{I} in the presence of boronic acid. Facile elimination of the Cu^{III} species delivers the C–N-coupled product. The results presented herein not only provide a reliable and efficient protocol for the synthesis of 2,5-disubstituted tetrazoles, but most importantly, the mechanistic results would have broad implications for the de novo design and development of new methods for Cu-catalyzed coupling reactions.

Introduction

Transition-metal-catalyzed aryl C–N bond-forming reactions are one of the most popularly investigated reactions in modern organic synthesis because of the ubiquity of aromatic C–N bonds in a broad spectrum of areas including natural product, pharmaceutical, agrochemical, catalysis, coordination chemistry, and polymer science.[1] The complementary use of Buchwald–Hartwig[2] and Chan–Evans–Lam[3] (CEL) couplings allow for a flexible and efficient construction of C–N bonds from a rich variety of NH-containing substrates, including primary and second alkyl and aryl amines, amides, imides, ureas, carbamates, sulfonamides, and hydrazine derivatives. However, despite of all these significant progresses, the coupling reactions for electron-deficient azoles such as triazoles and tetrazoles remains a considerable challenging by using either approach.

Thus, alternative protocols for accessing triazoles through the 1,3-dipolar cycloaddition of an alkyne and an azide, that is, click-chemistry, have been well- developed.[4] However, the analogous reaction of an azide and a nitrile for the construction of tetrazoles is extremely difficult. Such a cycloaddition could proceed only intramolecularly[5] or required strong electron-deficient nitrile substrates such as acyl cyanides and sulfonyl cyanides if the intermolecular version is under consideration.[6] Recently, Jiao disclosed a straightforward method for accessing tetrazoles from the simple styrene derivatives and $TMSN_3$.[7] In addition, the Pd-catalyzed Suzuki–Miyaura cross-coupling of 5-halo-1-aryl(alkyl)tetrazoles has also been reported.[8]

Although these methods have significantly advanced the synthesis of 1,5-disubstituted tetrazoles, more efficient and reliable protocols remain highly desirable because of the broad utility of tetrazole derivatives.[1] Moreover, the methods for the synthesis of 2,5-disubstituted tetrazoles are neither general nor practical. The Kakehi tetrazole synthesis[9] using aldehydes required several synthetic steps. Alternatively, the Pd- or Cu-catalyzed N-2-arylation of 5-substituted tetrazoles has been investigated [Eq. (1)].[10]



M = SnR_3, Na X = BF_4, Cl (1)

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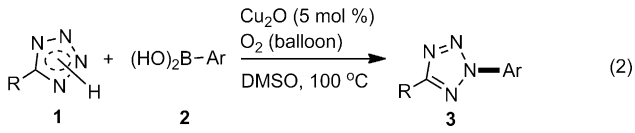
However, these methods necessitated the conversion of the tetrazoles into the more reactive N-metalated tetrazoles (M = SnR_3 and Na) prior to coupling. Moreover, diaryliodonium salts were used as the coupling partners. As a result, such methods are not only operationally tedious, but also generate stoichiometric amounts of toxic wastes such as organotin and aryliodide. In addition, high catalyst-loading was required in many cases. As a structural motif featuring the presence of four nitrogen atoms in a five-membered aromatic ring, tetrazoles exhibit unique physical and chemical nature. They can serve as metabolically stable surrogates of carboxylic acid group.[11] More importantly, they exhibit not only interesting biological properties but also good resistance against biological degradation.[12] Furthermore, terazoles are highly stable under a wide range of chemical environments[13] such as strong basic/acidic, and oxidizing/reducing conditions. Therefore, tetrazoles should find ample applications in a broad spectrum of areas if methods for facile synthesis of such compounds are established. In fact, a number of previous works have exemplified the importance of tetrazole compounds in materials science,[14] pharmaceutical,[15] and biological applications[16].



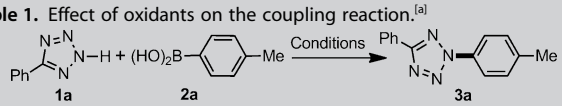
(2)

With our constant interest in the use of first row transition-metal-catalyzed cross-couplings of boron compounds,[17] we have previously developed a simple, clean, and highly efficient protocol that allows for flexible synthesis of 2,5-disubstituted tetrazoles through the direct coupling of H-tetrazoles and nontoxic boronic acids in a regiospecific manner [Eq. (2)].[18] The reaction proceeded in high yields in the presence of only 5 mol% of [Cu_2O] catalyst under oxygen in DMSO solvent at 100 °C. As the most important advantage, the protocol avoids the use of metalated tetrazoles and high-valent iodonium salts as reactants. In addition, external bases, ligands, and other additives routinely used in classic CEL couplings were not needed. After establishing the most practical and efficient method, we became interested in why the conventionally challenging reaction could indeed proceed so efficiently in such a simple system. Therefore, we initiated an in-depth study toward clarifying the reaction mechanism. Such an investigation would be valuable not only for a deeper understanding of CEL coupling, but also would have further implications for the de novo design and development of new methods for Cu-catalyzed coupling reactions. The important results will be presented herein.

Results and Discussion

In an early report by Lam and co-workers,[19] the Cu-mediated cross-coupling of 5-phenyltetrazole **1a** and 4-methyphenyl boronic acid **2a** was investigated (Table 1). An extensive optimization of various reaction parameters including catalyst, base, solvent, reaction time, and atmosphere, afforded the coupled product **3a** in 26% yield with the presence of 1.5 equiv of [$Cu(OAc)_2$] and 3.0 equiv of pyridine base. Although the outcome was less satisfactory, this preliminary result provided an important clue for the direct coupling of tetrazole and boronic acid by employing copper catalysts. In our initial study, we examined the effect of the oxidants on the reaction. An extensive screening of organic and inorganic oxidants showed that although most of the oxidants proved to be futile, four organic oxidants, [bis(trifluoroacetoxy)iodo]benzene (PIFA), (diacetoxyiodo)benzene (PIDA), benzoyl peroxide (BPO), and *meta*-chloroperbenzoic acid (*m*CPBA), could provide the desired products (Table 1). Notably, the yield of 2,5-disubstituted product **3a** could be increased to 52% in the presence of PIFA (Table 1, entry 1).

Table 1. Effect of oxidants on the coupling reaction.[a]



Entry	Oxidant [(equiv)]	Yield [%][b]
1	PIFA (2.0)	52
2	PIDA (2.0)	< 30[c]
3	BPO (1.0)	< 19[c]
4	*m*CPBA (1.0)	< 34[c]

[a] Reaction conditions: tetrazole **1a** (0.5 mmol, 1.0 equiv), boronic acid **2a** (0.6 mmol, 1.2 equiv), [$Cu(OAc)_2$] (0.5 mmol, 1.0 equiv), pyridine (1.5 mmol, 3.0 equiv), in DMF (4 mL) under nitrogen at 120 °C for 12 h. [b] Yield of the isolated product. [c] Contaminated by some inseparable impurities.

Having found a promising oxidant, we then examined the effect of solvents and bases (Table 2). Disappointingly, screening of various solvents revealed that only aprotic polar DMF and *N*,*N*-dimethylacetamide (DMAc) were the best solvents to afford the products in moderate yields (Table 2, entries 1 and 2). Other solvents gave only poor yields (Table 2, entries 3–6) or completely ineffective. Attempted improvement of the yield by varying the base was also fruitless. In most of the cases, replacement of pyridine by a range of inorganic and organic bases gave only a trace amount of product (data not shown).

Table 2. Effect of solvents on the coupling reaction of **1a** and **2a**.[a]

Entry	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	DMF	120	12	52
2	DMAc	120	12	43
3	DMSO	120	12	17
4	*t*BuOH	90	24	20
5	THF	80	24	22
6	DCE	80	24	31

[a] Reaction conditions: tetrazole **1a** (0.5 mmol, 1.0 equiv), boronic acid **2a** (0.6 mmol, 1.2 equiv), [$Cu(OAc)_2$] (0.5 mmol, 1.0 equiv), PIFA (1.0 or 2.0 equiv), pyridine (1.5 mmol, 3.0 equiv), in solvent (4 mL) under nitrogen. [b] Yield of the isolated product; DMAc = *N*,*N*-dimethylacetamide.

Table 3. Effect of copper salts on the coupling reaction of **1a** and **2a**.[a]

Entry	Cu salt [mol%]	Oxidant [(equiv)]	*t* [h]	Yield[b] [%]
1	[CuI] (100)	PIFA (2.0)	38	trace[c]
2	[CuBr] (100)	PIFA (2.0)	38	trace[c]
3	[CuCl] (100)	PIFA (2.0)	14	trace[c]
4	[$CuCl_2$] (100)	PIFA (1.0)	24	trace[c]
5	[$Cu(acac)_2$] (100)	PIFA (1.0)	24	trace[c]
6	[$Cu(OTf)_2$] (100)	PIFA (1.0)	12	47
7	[$Cu(OAc)_2$] (100)	PIFA (1.0)	12	52
8	[Cu_2O] (100)	PIFA (1.0)	24	60
9	[Cu_2O] (100)	air	24	50
10	[Cu_2O] (100)	air	24	67[d]

[a] Reaction conditions: tetrazole **1a** (0.5 mmol, 1.0 equiv), boronic acid **2a** (0.6 mmol, 1.2 equiv), Cu salt (0.5 mmol, 1.0 equiv), PIFA (1.0 or 2.0 equiv), pyridine (1.5 mmol, 3.0 equiv), in DMF (4 mL) under nitrogen at 120 °C. [b] Yield of the isolated product. [c] Monitored by TLC. [d] 2.0 equiv of **2a** was used; acac = acetylacetonate.

Table 4. Optimization of the reaction conditions.[a]

Entry	[Cu_2O] [mol%]	Py. [equiv]	Solvent	*T* [°C]/*t* [h]	Yield [%][b]
1	100	3.0	DMF	120/24	77
2	100	3.0	DMSO	120/24	92
3	50	3.0	DMSO	120/24	96
4	50	3.0	DMSO	120/12	95
5	20	3.0	DMSO	1200.5	95
6	10	3.0	DMSO	120/1	92
7	5	2.0	DMSO	100/5.5	94
8	5	2.0	DMSO	80/24	n.c.[c]
9	5	–	DMSO	100/4	95[d]
10	5	–	DMF	100/24	27
11	5	–	DMSO	100/48	12[e]
12	–	–	DMSO	100/28	n.r.[f]

[a] Reaction conditions: tetrazole **1a** (0.5 mmol, 1.0 equiv), boronic acid **2a** (1.0 mmol, 2.0 equiv), [Cu_2O], pyridine in solvent (4 mL). [b] Yield of the isolated product. [c] The reaction was not completed. [d] Pyridine base was omitted. [e] The reaction was carried out under nitrogen. [f] No reaction in the absence of [Cu_2O].

Next, by fixing the PIFA as the oxidant, pyridine as the base, and DMF as the solvent, we carried out a survey of copper salts (Table 3). Among a range of Cu^{I} and Cu^{II} salts (Table 3, entries 1–8), only [$Cu(OTf)_2$], [$Cu(OAc)_2$], and [Cu_2O] could affect the reaction to give the product in moderate to moderately high yields (Table 3, entries 6–8); the best result was afforded by [Cu_2O] in 60% yield (entry 8).

Although the result was still not satisfactory after the exhaustive optimization, a yield of 60% was a significant improvement compared with the reported result.[19] More to the point, we recognized through these studies that a suitable choice of solvent, oxidant, and base would be essentially important for achieving an efficient cross-coupling. On the other hand, we were also aware that although the yield might be improved to a satisfactory level after further optimization, practical application of the method under the current conditions would be reduced due to the use of stoichiometric amounts of copper catalyst, organic oxidant, and pyridine base. As such, our efforts were then devoted to simplifying the reaction conditions. Delightedly, we found that the coupled product **3a** could be obtained in 50% yield when the reaction was carried out under air in the absence of PIFA (Table 3, entry 9). Increase of boronic acid **2a** from 1.2 to 2.0 equiv could improve the yield to 67% (Table 3, entry 10).

With this highly promising result in hand, we re-examined the reaction parameters by omitting the organic oxidant from the reaction system. After a brief optimization, we found that the yield of **3a** could be improved to 77% when the reaction was carried out under oxygen and in the presence of 2.0 equiv of boronic acid (Table 4, entry 1). More pleasingly, an excellent yield (92%) was obtained by replacing DMF with DMSO (Table 4, entry 1 vs. 2). Here, the use of undistilled DMSO as the solvent makes the reaction more convenient for operation. Thus, through this extensive optimization, we achieved the direct coupling of tetrazole and boronic acid in high yield with the presence of 100 mol% [Cu_2O] and 3.0 equiv of pyridine base under oxygen in DMSO at 120 °C. At this juncture, we became further interested in whether the reaction could proceed in a more efficient manner, that is., with a catalytic amount of [Cu_2O] and less equivalents of pyridine. Fortunately, a systematic examination on these parameters exemplified that the conditions could be considerably simplified. Namely, the loading amount of [Cu_2O] catalyst could be reduced to as low as 5 mol% and the pyridine base could be entirely omitted from the reaction system (Table 4, entries 3–9). In addition, the reaction temperature could be further lowered to 100 °C. Under such simplified conditions, the reaction was completed within 4 h to afford the coupled product **3a** in 95% yield (Table 4, entry 9). As a comparison, the reaction was rather sluggish in DMF solvent (Table 4, entry 10) or under nitrogen atmosphere even if the reaction time was elongated (Table 4, entry 11). In addition, the product was not observed in the absence of the [Cu_2O] catalyst (Table 4, entry 12). These results clearly demonstrated that DMSO and oxygen is of crucial importance for the transformation.

The crucial importance of a combination use of DMSO as solvent and oxygen as oxidant for the direct coupling of tetrazoles and boronic acids was firmly exemplified by the highly effective coupling of **1a** and **2a** by employing an array of other copper salts. As shown in Table 5, rapid conversion as well as excellent yield was observed not only for various Cu^{I} (entries 1–3), but also for several Cu^{II} salts (entries 4–6), albeit

Table 5. Catalytic efficiency of various copper salts on the coupling reaction of **1a** and **2a** in DMSO under oxygen.[a]

Entry	Cu salt [mol%]	*t* [h]/*T* [°C]	Yield [%][b]
1	[CuI] (10)	4/100	98
2	[CuBr] (10)	3.5/100	90
3	[CuCl] (10)	4/100	85
4	[$Cu(acac)_2$] (10)	4/100	90
5	[$Cu(OAc)_2$] (10)	3.5/100	92
6	[CuO] (10)	120/100	87

[a] Reaction conditions: tetrazole **1a** (0.5 mmol, 1.0 equiv), boronic acid **2a** (1.0 mmol, 2.0 equiv), copper salt (10 mol%) under oxygen in DMSO (4 mL) at 100 °C. [b] Yield of the isolated product.

[CuO] required a prolonged reaction time (entry 6). In stark contrast, these salts were inactive or displayed only poor activity even presented in stoichiometric amount if either DMSO or oxygen was replaced by other solvents or oxidants (Tables 1–3, and entries 10 and 11 in Table 4).

Now, through a careful and patient investigation, we have established a very simple and robust methodology for the regiospecific synthesis of 2,5-disubstituted tetrazoles through the direct coupling of H-tetrazole and boronic acid. Most significantly, the method exhibited a broad generality and reliability that allowed for the diverse synthesis of 2,5-disubstituted tetrazoles through a flexible combination of various tetrazoles and boronic acids (Table 6).[18] Undoubtedly, the success on this conventionally challenging reaction should expand significantly the original scope of CEL coupling.

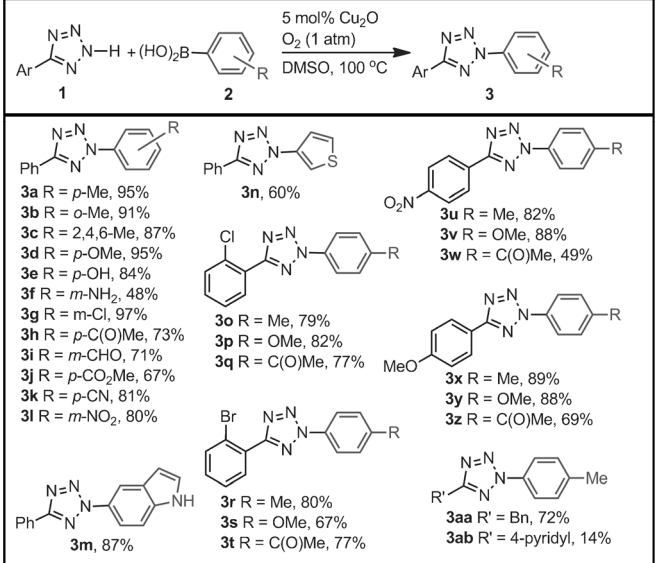
Next, to gain a deeper understanding on this transformation, we carried out the mechanistic investigations. Although plenty of mechanisms for the copper-catalyzed CEL coupling have been proposed based on the empirical observations since its discovery,[3] systematic investigations have been rarely carried out. In 2009, Stahl and co-workers[20] reported the first detailed mechanistic study on the $[Cu(OAc)_2]$-catalyzed C–O bond-forming reaction using tolylboronic ester and MeOH as substrates. In another report in 2010,[21] Tromp and co-workers studied the mechanism of a Cu^{II} complex, $[Cu(OH)(tmeda)]_2{\cdot}Cl_2$ (tmeda = tetramethylethylenediamine), -catalyzed cross-coupling of phenylboronic acid with imidazole using a multitechnique approach.

Although these systematic studies, along with those empirical proposals, provided valuable information for an in-depth understanding of CEL coupling, they are inconvincible when used to elucidate the reaction mechanism of tetrazoles and boronic acids because none of them has considered the effect of solvent; whereas we have unambiguously demonstrated that solvent is crucial for effective reaction herein. In addition, the critical role played by oxygen also awaits clarification because, unlike the coupling of imidazole and boronic acid,[21] oxygen is indispensable in promoting the coupling of tetrazoles and boronic acids. As such, the coupling of tetrazoles and boronic acids should undergo a different reaction model from those proposed in literatures for the coupling of alcohols or electron-rich azoles with boronic acids. Therefore, we carried out a detailed investigation into the reaction mechanism of tetrazoles and boronic acids.

Initial control experiments showed that heating the mixture of $[Cu_2O]$ and boronic acids in DMSO resulted in a complex mixture generated from the homocoupling, protonolysis, and hydrolysis of boronic acids. In addition, the dehydrated boroxin might also be detected. In fact, these side-reactions were often observed in CEL coupling.[3] Interestingly, when $[Cu_2O]$ was stirred with a large excess of 5-phenyltetrazole **1a** (1:4 mol/mol) in DMSO, we observed two entirely different results depending on the reaction atmosphere. Namely, the particles of the brownish-red $[Cu_2O]$ remained almost unchanged under nitrogen after heating at 100 °C for over 12 h. In sharp contrast, the color of Cu_2O and **1a** mixture was changed gradually to sky-blue under oxygen (Figure S1 in the Supporting Information). The insoluble blue precipitates were collected by filtration and washed thoroughly with water and ethyl acetate. The dried powder was then analyzed by using various spectroscopic techniques.

The X-ray photoelectron spectroscopic (XPS) analysis revealed that the $2p^{3/2}$ binding energy of the copper species was 935.2 eV, indicating that the Cu^{I} species was oxidized to Cu^{II} under oxygen atmosphere (Figure 1a). The oxidative generation of Cu^{II} species was strongly supported by the comparison experiment using $[Cu(OAc)_2]$. This Cu^{II} salt could also form blue-colored complexes with tetrazole **1a** either under nitrogen or under oxygen, and exhibited identical 2p binding energy (Figure 1b, the $2p^{3/2}$ binding energy was 934.9 eV) to that of the complex prepared from $[Cu_2O]$ and **1a** under oxygen. Furthermore, the solid state NMR spectroscopic studies showed that both complexes formed from $[Cu_2O]$ and $[Cu(OAc)_2]$ have the same spectral data, which implies that the two complexes possess the same structure (Figure 2a and b).

Table 6. Cu-catalyzed coupling of various tetrazoles **1** with boronic acids **2**.[a]



[a] See ref. [18] for detailed results and discussion.

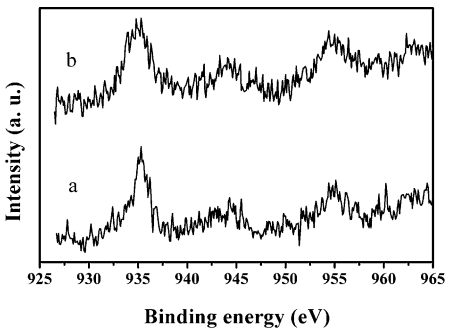


Figure 1. XPS spectra of: a) the complex from $[Cu_2O]$ and tetrazole **1a**; and b) the complex from $[Cu(OAc)_2]$ and **1a**.

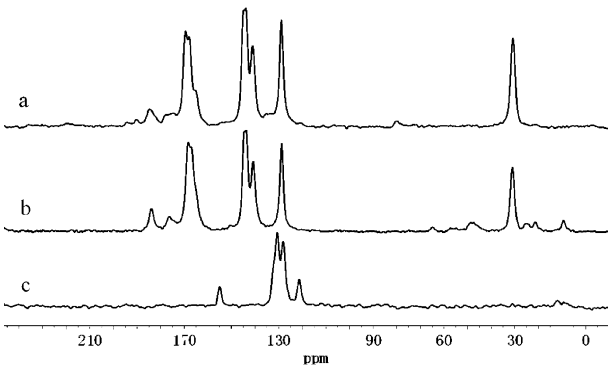


Figure 2. Solid state ^{13}C NMR spectra of: a) the complex from $[Cu_2O]$ and tetrazole **1a**; b) the complex from $[Cu(OAc)_2]$ and tetrazole; c) free **1a**.

In the ^{13}C NMR spectra, a set of signals at the aromatic region appeared. In addition, a singlet at $\delta = 30.5$ ppm was also presented. These observations suggested that the Cu^{II} center connects with tetrazole **1a** and the DMSO molecule. Moreover, compared with the free **1a** (Figure 2c), the signals of the phenyl ring in the Cu^{II} complex are shifted largely downfield of up to about $\delta = 45$ ppm. Such a large shift implies that there is a strong bond affinity between tetrazole **1a** and Cu^{II} species. The structural identity of the two complexes was further confirmed by the powder X-ray diffraction (XRD; Figure 3). Both complexes exhibited exactly the same XRD patterns.

In good agreement with the NMR data and XRD patterns, elemental analysis showed that both the complexes derived from $[Cu_2O]$ and $[Cu(OAc)_2]$ have identical element contents consisting of Cu, tetrazole **1a**, and DMSO in 1:2:1 ratio (Table 7). These results indicate that DMSO may serve as a ligand to coordinate with Cu^{II}. In fact, DMSO has been frequently used as a common ligand in coordination chemistry with various transition metals.[22] IR spectroscopic testing confirmed that the strong and broad bands around 2500–3100 cm^{-1}, due to the N–H in free tetrazole **1a** were missing in both Cu complexes (data not shown), indicating the loss of hydrogen atom in tetrazole during the complex formation.

Thus, on the basis of the XPS, NMR spectroscopy, XRD, IR, and elemental analysis, we may confirm that the $[Cu_2O]$ and $[Cu(OAc)_2]$ formed the same complexes with a common unit formula as $[(Cu^{2+})\{(\mathbf{1a})^-\}_2(dmso)]$. Namely, a Cu^{II} center connected with two tetrazole anions through a Cu–N covalent bond and one DMSO molecule through a coordination bond. The deduced structure of the complex was strongly supported by the mass analysis (Figure S2 in the Supporting Information). MALDI-TOF mass spectroscopic study on the copper complex revealed a strong peak at *m/z* 353.0, corresponding to the $[(Cu^{2+})\{(\mathbf{1a})^-\}_2]$ complex (calcd *m/z* 353.0). DMSO was lost due to the relatively weak coordination bond. In addition, a rather weak peak at *m/z* 561.0 appeared. This single peak can be assigned to a $[(Cu^{2+})_2\{(\mathbf{1a})^-\}_3]$ species (calcd *m/z* 561.0) due presumably to the recombination of fragment ions. As a result, the comprehensive spectroscopic study not only clarified the structure of the copper complex, but also most interestingly, we have found an unprecedented reaction that the Cu^{I} species could form a Cu^{II} complex through an oxidative copper amination. To facilitate the following discussion, the Cu^{II} complexes formed from $[Cu_2O]$ and $[Cu(OAc)_2]$ were defined as **CuT_2D-1** and **CuT_2D-2**, respectively (T = tetrazole anion, and D = DMSO). Here, it should be mentioned that although we have confirmed the unit structure of the complexes, their poor solubility makes it difficult to confirm whether the complexes exist in the monomeric or polymeric form. Indeed, we noted that the tetrazole-based Cu^{II} complexes have been reported in 1961.[23] However, little is known about the nature of such type of complexes due to their poor solubility.

Having clarified the structure of the copper complexes, we then investigated the coupling reaction of **CuT_2D-1** complex with boronic acid **2a**. For parallel comparison, the reaction of **CuT_2D-2** was also performed (Table 8). Interestingly, we found that when **CuT_2D-1** or **CuT_2D-2** was treated with boronic acid **2a** in 1:4 molar ratio (corresponding to 1:2 ratio of **1a**/**2a** as used in the optimized conditions; Table 4), the coupled product **3a** was obtained in about 25% yield under nitrogen based

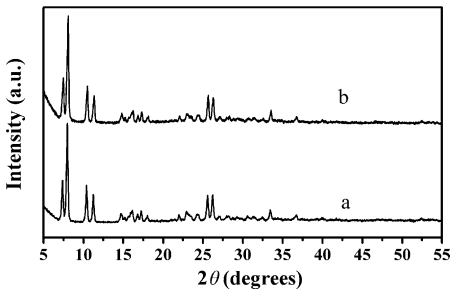


Figure 3. Powder X-ray diffraction pattern of: a) the complex from $[Cu_2O]$ and tetrazole **1a**; and b) the complex from $[Cu(OAc)_2]$ and **1a**.

Table 7. Elemental analysis data of copper complexes formed from $[Cu_2O]$ (**CuT_2D-1**) and $[Cu(OAc)_2]$ (**CuT_2D-2**).[a]

Cu Complexes	Cu [%]	C [%]	H [%]	N [%]	S [%]
CuT_2D-1	14.64	44.03	3.54	25.77	7.39
CuT_2D-2	15.27	44.00	3.57	25.84	7.22
$[(Cu^{2+})\{(\mathbf{1a})^-\}_2(dmso)]$	14.71	44.49	3.73	25.94	7.42

[a] Average value from two batches of samples, each batch was measured three times.

Table 8. Coupling reaction of Cu complexes with boronic acid **2a**.[a]

Entry	Cu Complex	Atmosphere	*t* [h]	Yield [%][b]
1	**CuT_2D-1**	N_2	13	23[c]
2	**CuT_2D-2**	N_2	13	25[d]
3	**CuT_2D-1**	O_2	13	49[e]
4	**CuT_2D-2**	O_2	13	52[d]

[a] Reaction conditions: Cu complex (0.25 mmol, 1.0 equiv), boronic acid **2a** (1.0 mmol, 4.0 equiv) in DMSO (4 mL) at 100 °C. [b] Yield of the isolated product based on the equiv of tetrazole anions in the copper complexes; 1 mol of complex contains 2 mol of tetrazole anions. [c] Average yield for three runs. [d] Average yield for two runs. [e] Average yield for four runs.

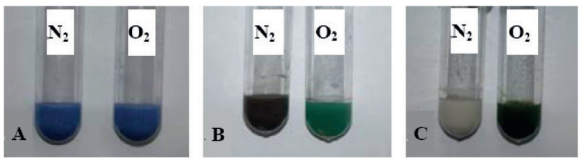


Figure 4. Color changes of the reaction mixture of **CuT_2D-1** with boronic acid **2a** under nitrogen (left) and oxygen (right): A) starting mixture; B) heating after 2 h; and C) heating after 10 h.

on the equivalents of tetrazole anions in the complexes (Table 8, entries 1 and 2). However, the yields were increased to about 50% under oxygen (Table 8, entries 3 and 4). The unreacted tetrazole **1a** could be recovered almost quantitatively after cracking the copper complexes with diluted aqueous HCl, indicating that no other side reaction occurs. The results exhibited good duplicability for several trials. Correlated with the reaction yields, an apparently different color change was observed for the reaction systems under the different atmosphere. As shown in Figure 4, with the progress of the reaction, the blue colored starting mixture of **CuT_2D-1** (or **CuT_2D-2**) and boronic acid **2a** (Figure 4A or Figure S3 in the Supporting Information) changed to dark gray under nitrogen (Figure 4B, left). In stark contrast, the color turned grass-green under oxygen (Figure 4B, right). Further heating of the reaction vessels resulted in an off-white (Figure 4C, left) and a dark-green-colored mixture (Figure 4C, right) for the nitrogen and oxygen systems, respectively. XPS analyses of the precipitates recovered from the reaction mixture revealed that the redox state of the Cu^{II} species under oxygen atmosphere remained unchanged. The $2p^{3/2}$ binding energy was 935.1 eV (Figure 5, spectrum c). This value is identical to that of the starting complex **CuT_2D-1** or **CuT_2D-2** (Figure 1). In contrast, the $2p^{3/2}$ binding energy was changed to 931.7 eV for the insoluble residues recovered from the reaction mixture under nitrogen (Figure 5, spectrum d). This data strongly evidenced that the Cu^{II} species was converted into Cu^{I} during the reaction under nitrogen. As an important hint, the formation of Cu^{I} suggested that the product was formed through the reductive elimination of Cu^{III} rather than Cu^{II} intermediates, since Cu^{0} was not detected.

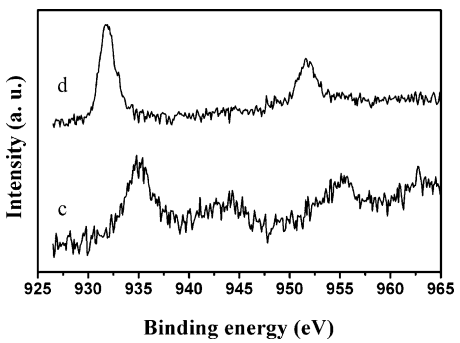
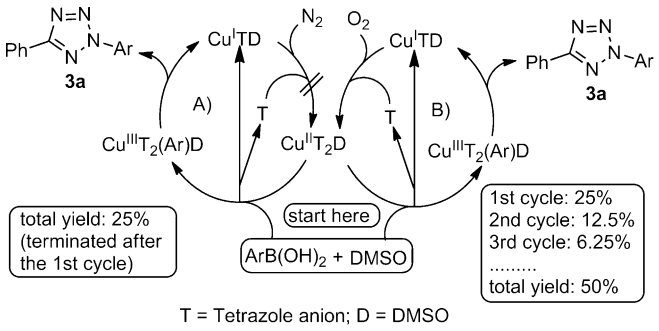


Figure 5. XPS spectra of the insoluble residues recovered from the reaction mixture of the copper complex and boronic acid **2a** under: c) oxygen, and d) nitrogen.

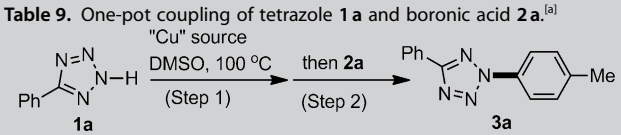


Scheme 1. Proposed reaction processes of Cu^{II} complex with boronic acid under nitrogen (**A** cycle) and oxygen (**B** cycle).

On the basis of the above experimental results and some recent compelling reports by the groups of Stahl,[20,24] Tromp,[21] and Ribas,[25] who demonstrated that Cu^{II} is ready to undergo disproportionation to generate Cu^{III} and Cu^{I}, we could propose a reasonable explanation to the results obtained in Table 8. As illustrated in Scheme 1, in the presence of boronic acid **2a** and DMSO, disproportionation of 1.0 equiv of the Cu^{II} complex **CuT_2D-1** (or **CuT_2D-2**) may proceed to generate 0.5 equiv of [$Cu^{III}T_2$(Ar)D], [Cu^{I}TD], and T, respectively, either under nitrogen or under oxygen. Subsequently, the [$Cu^{III}T_2$(Ar)D] complex thus formed undergoes facile reductive elimination to deliver 0.5 equiv of product **3a** and Cu^{I}T, respectively. At this juncture, the reaction is terminated if the reaction is carried out under nitrogen because the Cu^{I}T cannot be oxidized to Cu^{II} in the absence of oxidant (**A** cycle). As a result, only a quarter equivalent of tetrazole anions in **CuT_2D-1** (or **CuT_2D-2**) can be converted into the product **3a**. Thus, the maximum theoretical yield under nitrogen is 25%. Alternatively, if the reaction is carried out under oxygen (**B** cycle), the "side-products" [Cu^{I}TD] and 0.5 equiv of **T** formed in the first cycle could regenerate 0.5 equiv of [$Cu^{II}T_2$D] through an oxidative copper amination reaction.[26] Then, disproportionation of the regenerated [$Cu^{II}T_2$D], followed by reductive elimination to give 0.25 equiv of **3a** associated with the formation of 0.25 equiv of "side-products" [Cu^{I}TD] and T. Such a reaction circulates round by round until [$Cu^{II}T_2$D] cannot be formed, and affords theoretically $(0.5)^{n+1}$ equiv of product in each reaction cycle (n = the number of the reaction cycles). Consequently, the maximum theoretical yield of the coupled product **3a** under oxygen is 50% as a sum of $(0.5)^2+(0.5)^3+(0.5)^4+\ldots+(0.5)^{n+1}$.

To further confirm the reaction model as shown in Scheme 1, we carried out some comparison reactions through a one-pot operation (Table 9). Namely, a mixture of [Cu_2O] and tetrazole **1a** in 1:4 or [$Cu(OAc)_2$] and **1a** in 1:2 molar ratio (the ratio of Cu species to **1a** = 1:2) was stirred at 100 °C under a given atmosphere for 48 h to ensure the complete formation of 1:2 copper complex (step 1). Then boronic acid **2a** was recharged in situ and the resulting mixture was continuously heated for additional hours (step 2). Consequently, 21% and 25% of the coupled product **3a** were obtained, respectively, from [Cu_2O] and [$Cu(OAc)_2$] under nitrogen (Table 9, entries 1 and 2). On the other hand, 49% and 48% of **3a** were obtained,

Table 9. One-pot coupling of tetrazole **1a** and boronic acid **2a**.[a]



Entry	Cu salt	Atmos/*t* [h] step 1	Atmos/*t* [h] step 2	Yield **3a** [%][b]
1	$[Cu_2O]$	O_2/48	N_2/23	21
2	$[Cu(OAc)_2]$	N_2/48	N_2/23	25
3	$[Cu_2O]$	O_2/48	O_2/23	49
4	$[Cu(OAc)_2]$	N_2/48	O_2/23	48

[a] Reaction conditions: Cu_2O (0.25 mmol) or $[Cu(OAc)_2]$ (0.5 mmol), tetrazole **1a** (1.0 mmol) in DMSO (4 mL) at 100 °C for 48 h under the corresponding atmosphere as in the Table; then, boronic acid **2a** (1.2 mmol) was recharged in situ and stirred for 23 h under the atmosphere as assigned in the Table. [b] Yield of the isolated product based on tetrazole.

Table 10. Coupling reaction of tetrazole **1a** and boronic acid **2a** (or the corresponding boroxin) in the presence of a catalytic amount of Cu complexes.[a]

Entry	Cu complex	Boron source	Solvent	*T* [°C]	Yield **3a**[b] [%]
1	**CuT_2D-1**	**2a**	DMSO	100	89
2	**CuT_2D-2**	**2a**	DMSO	100	79
3	**CuT_2D-1**	**2a**	DMSO	80	90
4	**CuT_2D-1**	**2a**	DMSO	70	trace[c]
5	**CuT_2D-1**	**2a**	DMF	100	57
6	**CuT_2D-1**	**2a**	DMSO	100	93[d]
7	**CuT_2D-1**	boroxin	DMSO	100	94[d]
8	**CuT_2D-1**	**2a**	DMSO	100	93[d,e]
9	**CuT_2D-1**	boroxin	DMSO	100	93[d,e]
10	**CuT_2D-1**	**2a**	DMSO	100	87[f]

[a] Reaction conditions: tetrazole **1a** (0.4 mmol), boronic acid **2a** (1.0 mmol), **CuT_2D-1** or **CuT_2D-2** (5 mol%) under oxygen in solvent (4 mL) for 10 h. [b] Yield of the isolated product. [c] Monitored by TLC. [d] Dried DMSO was used; [e] 1.0 equiv of H_2O was added; [f] 1.0 equiv of TEMPO was added.

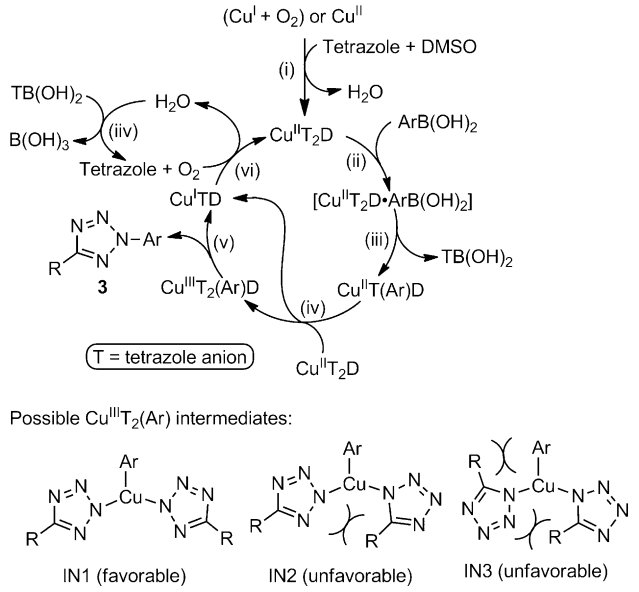
respectively, when the reaction was carried out under oxygen (Table 9, entries 3 and 4). These results were in very good agreement with those obtained from the direct reaction of **CuT_2D-1** and **CuT_2D-2** complexes with boronic acid **2a** (Table 8), and further reinforced the rationality of the proposed reaction model.

From these experiments, we can draw several important conclusions: 1) disproportionation of Cu^{II} to Cu^{III} and Cu^{I} species can proceed without the assistance of oxygen since about 25% of product is formed under nitrogen; 2) the cleavage of the Cu–N bond in a copper complex having only one tetrazole anion, for example, $[Cu^{I}TD]$ or $[Cu^{II}TDX]$ formed in the reaction cycle, is difficult during the reaction. Otherwise, a Cu^{II} complex possessing two tetrazole anions such as $[Cu^{II}T_2D]$ could be reformed through the cleavage and reunion of Cu–N bond under oxygen, and ultimately, leading to the production of **3a** in higher yield than 50%; 3) the generation of the cross-coupled product from a copper complex with whichever redox state, for example, Cu^{I} to Cu^{III}, but containing only one tetrazole anion is difficult. Otherwise, the yield of **3a** should be also higher than 50%. As such, a high yield reaction is conceived to be carried out in such a system that is capable of generating the $[Cu^{II}T_2D]$ species sustainably during the reaction.

Accordingly, we investigated the reaction of tetrazole **1a** and boronic acid **2a** by using a catalytic amount of **CuT_2D-1** or **CuT_2D-2** complexes as catalysts under oxygen. Based on the reaction cycle illustrated in the **B** cycle in Scheme 1, such a system could ensure a contiguous formation of the $[Cu^{II}T_2D]$ intermediate from a catalytic amount of $[Cu^{I}T]$ species generated in the reaction cycle and excess **1a** added initially through the oxidative copper amination process. As expected, the coupling reaction of tetrazole **1a** and boronic acid **2a** could really proceed very efficiently in the presence of 5 mol% **CuT_2D-1** or **CuT_2D-2** (Table 10, entries 1 and 2). A high yield was also obtained when the reaction was carried out at 80 °C (Table 10, entry 3). However, the reaction hardly takes place when the reaction temperature was decreased to lower than 70 °C (Table 10, entry 4), indicating that disproportionation of Cu^{II} may be the rate-limiting step in the reaction cycle. In addition, the yield was diminished markedly when DMF was used instead of DMSO (Table 10, entry 5). This observation, again, demonstrated that the use of DMSO as solvent is crucial for accelerating the reaction through its coordination effect with copper.

For the disproportionation of Cu^{II}, Tromp and co-workers[21] have suggested that adventitious water was essential to promote the transfer of phenyl group from boronic acid to the Cu^{III} center. However, we demonstrated that the **CuT_2D-1**-catalyzed coupling of tetrazole **1a** with **2a** or its boroxin derivative could proceed very smoothly in the scrupulously dried DMSO solvent (Table 10, entries 6 and 7). Comparison studies showed that external addition of water to the reaction system do not influence the reaction (Table 10, entries 8 and 9). These results clearly exemplify that water is not essential for our reaction. On the other hand, since it has been proposed that the generation of phenyl radical is also possible through the homolytic splitting of boronic acid,[21,27] we wondered whether the coupling reaction proceeded through a radical pathway under our conditions. However, the control experiment by adding one equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) into the reaction system showed that the reaction proceeded uneventfully to give the product in 87% yield (Table 10, entry 10). The result clearly demonstrates that the phenyl radical does not participate in the reaction cycle.

Consequently, a variety of spectroscopic analyses combined with the comprehensive control experimental studies enable us to propose a plausible mechanism for the copper (either Cu^{I} or Cu^{II})-catalyzed cross-coupling of tetrazole and boronic acid (Scheme 2). The reaction initiates with the formation of a Cu^{II} complex possessing a unit formula of $[Cu^{II}T_2D]$ (step i, T = tetrazole anions; D = DMSO) either from Cu^{I} or Cu^{II} salts. Interestingly, we have demonstrated that the Cu^{I} undergoes an oxidative copper amination reaction with the presence of oxygen to generate the Cu^{II} complex. Then, transmetalation of the aryl group from boronic acid to $[Cu^{II}T_2D]$ delivers $[Cu^{II}T(Ar)D]$ through the intermediate $[Cu^{II}T_2D{\cdot}ArB(OH)_2]$



Scheme 2. Proposed reaction mechanism of Cu^{I}- and Cu^{II}-catalyzed direct-coupling of terazole and boronic acid.

(Scheme 2, steps ii and iii). Disproportionation of [Cu^{II}T(Ar)D] with another equiv of Cu^{II} generates the [Cu^{III}T$_2$(Ar)D] and [Cu^{I}TD] (step iv). Facile reductive elimination of [Cu^{III}T$_2$(Ar)D] yields the product **3** and [Cu^{I}TD] (step v). Finally, re-oxidative copper amination of [Cu^{I}TD] generated in steps iv and v by oxygen takes place to regenerate [Cu^{II}T$_2$D] (step vi). In the reaction cycle, tetrazole can be supplied either by the initially added materials or can be generated from TB(OH)$_2$ formed in step iii (step vii).

The regiospecific formation of 2,5-disubstituted tetrazole may be governed by the steric effect of the regioisomers of [Cu^{III}T$_2$(Ar)] intermediate. As illustrated in Scheme 2, three appreciable regioisomers **IN1**, **IN2**, and **IN3** may exist for [Cu^{III}T$_2$(Ar)]. Among these regioisomers, **IN1**, the Cu–N bond of which is formed at the N2 position of tetrazole, should present as the most favorable one due to having the smallest steric repulsion. As a result, the 2,5-disubstituted product is afforded. In comparison, **IN2** and **IN3**, the Cu–N bonds of which are connected at the N1 position of tetrazole, are unfavorable intermediates owing to the larger sterical repulsion. Consequently, the 1,5-disubstituted regioisomer cannot be formed. The hypothesis is strongly supported by the results of a detailed computational study,[28] which shows that the energy of **IN1** is about 3.5 kcal mol^{-1} lower than that of **IN2**, and about 7.3 kcal mol^{-1} lower than that of **IN3**.

Conclusion

Through a careful and patient study, we have developed a copper-catalyzed protocol that allows for the diverse synthesis of 2,5-disubstituted tetrazoles in a regiospecific manner. To compare with the very few Cu- or Pd-catalyzed methods,[10] in which metalated tetrazole and high-valent diaryliodonium salts were used as coupling partners, the protocol presented herein achieved the reaction through the direct coupling of tetrazoles and nontoxic boronic acids. Moreover, the reaction could be carried out simply in the presence of only 5–10 mol% of copper salts under oxygen in DMSO solvent. In addition, an array of Cu^{I} and Cu^{II} salts were demonstrated to be effective catalysts for this transformation. Thus, the new method offers a rich range of apparent advantages in terms of efficiency, simplicity, practicality, generality, and environmental impact. Most significantly, through a comprehensive spectroscopic studies and properly designed control experiments, we have clarified the critical role played by each component in the reaction mixture, which enabled us to establish a reasonable mechanism for the reaction. The most key points involved in the reaction cycle are the formation of a catalytically active Cu^{II} species through the oxidative copper amination of Cu^{I} and the apparent coordination effect of DMSO solvent. Furthermore, we have also clearly demonstrated that the disproportionation of Cu^{II} can proceed without the assistance of oxygen, and that a free radical species does not participate in the cycle. We believe this unprecedented finding will be valuable for a clear understanding of CEL reaction as well as for the de novo design and development of new methods for Cu-catalyzed coupling reactions.

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Keywords: boronic acid · copper · C–N bond formation · cross-coupling · tetrazole

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