

# Copper-Catalyzed Intramolecular C–H Alkoxylation of Diaryltriazoles: Synthesis of Tricyclic Triazole Benzoxazines

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**ABSTRACT:** An efficient copper-catalyzed intramolecular C–H alkoxylation of 1,4-disubstituted 1,2,3-triazoles has been developed. The chemistry was applied to a wide range of substrates, generating tricyclic benzoxazine-fused 1,2,3-triazoles in good yields. Mechanistic studies suggest that a radical pathway may be involved in this transformation. The triazole products were found to exhibit strong antifungal activity against ginseng root-rot disease, demonstrating their potential as a scaffold in medicinal chemistry research.

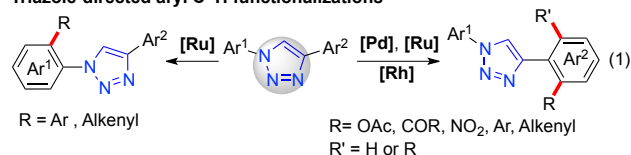
1,2,3-Triazoles are readily accessible heterocycles that have found applications across organic chemistry, materials science, medicinal chemistry, and chemical biology.<sup>1–4</sup> Novel triazole derivatives, such as polycyclic triazoles or those functionalized with additional heteroatom substituents, are of considerable interest due to potential uses in such fields. For example, while oxygenated sidechains can be introduced into 1,2,3-triazoles via cycloaddition-based approaches,<sup>5</sup> triazoles in which an oxygen atom is directly attached to the heterocyclic core are significantly less common,<sup>6</sup> not least as a cycloaddition disconnection would require the use of an ynol ether. Heteroatom substituents could significantly influence the physicochemical properties of the triazole ring, and as such methods for the synthesis of oxygenated triazoles are highly desirable.

Transition-metal-catalyzed C–H functionalization is one of the most powerful methods to construct new C–X bonds on aromatic and heteroaromatic rings,<sup>7</sup> and triazoles have been widely used as directing groups for C–H functionalization processes (Scheme 1, eq. 1).<sup>8</sup> In contrast, there are few strategies for direct C–H activation on the triazole ring itself, examples being limited to Pd-catalyzed alkenylation and arylation at the C5 position (Scheme 1, eq. 2),<sup>9</sup> and to our previous report of an intramolecular silver-catalyzed C5-acyloxylation that affords fused triazole isochromenones (Scheme 1, eq. 3).<sup>10</sup>

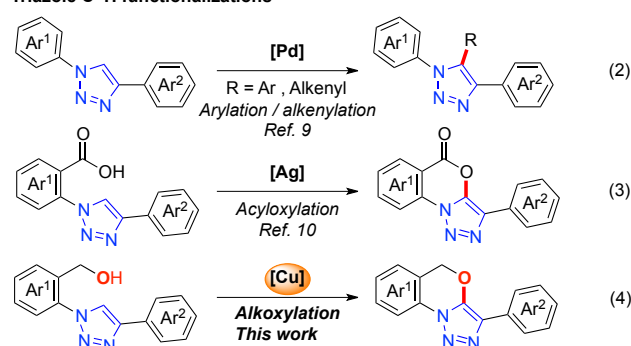
In light of the importance of novel heterocyclic scaffolds in medicinal chemistry,<sup>11</sup> we targeted the development of other methods to achieve triazole C–H functionalization. Here we report an efficient copper-catalyzed intramolecular C–O bond formation at the 5-position of the 1,2,3-triazole ring to generate tricyclic triazole-benzoxazines (Scheme 1, eq. 4), and insight into the mechanism of this process. Triazole-containing compounds have been shown to exhibit antifungal activity against pathogens such as *Candida albicans* SC5314, *Rhizoctonia solani*, *Gaeumannomyces graminis* and *Cylindrocarpon destructans*,<sup>12</sup> and we also report the antifungal properties of the fused tricyclic triazoles prepared in this work against ginseng root-rot disease, which demonstrates the potential

**Scheme 1. C–H Functionalization of 1,4-diaryl-1,2,3-triazoles.**

## Triazole-directed aryl C–H functionalizations



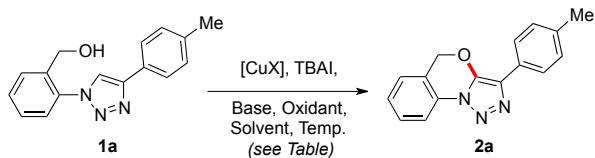
## Triazole C–H functionalizations



utility of this novel framework in biological settings.

At the outset of our studies, we selected 1,4-disubstituted 1,2,3-triazole **1a** as model substrate (Table 1). We questioned whether formation of an oxygen-centered radical could trigger C–O alkoxylation of the triazole ring, in light of a related base-free CuCl / (*t*-BuO)<sub>2</sub> mediated cyclization of (benz)imidazoles.<sup>13</sup> However, after some experimentation, we found that not only was a base required to achieve cyclization, but also the additive tetrabutylammonium iodide (TBAI), which in combination with peroxide oxidants is known to be an effective radical initiator.<sup>14</sup> Thus, in the presence of 20 mol% CuBr, 10 mol% TBAI, 1.5 equivalents of di-*tert*-butyl hydroperoxide (DTBP) and 4.0 equivalents of *t*-BuOLi in DCE at 120 °C under an N<sub>2</sub> atmosphere, the intramolecular triazole alkoxylation product **2a** was isolated in a pleasing 53% yield (Entry 1).<sup>15</sup> Other oxidants (*t*-butyl hydroperoxide (TBHP) or PhI(OAc)<sub>2</sub>) led to inferior results (Entries 2, 3), while a solvent screen showed a

**Table 1. Optimization of Reaction Conditions<sup>a</sup>**



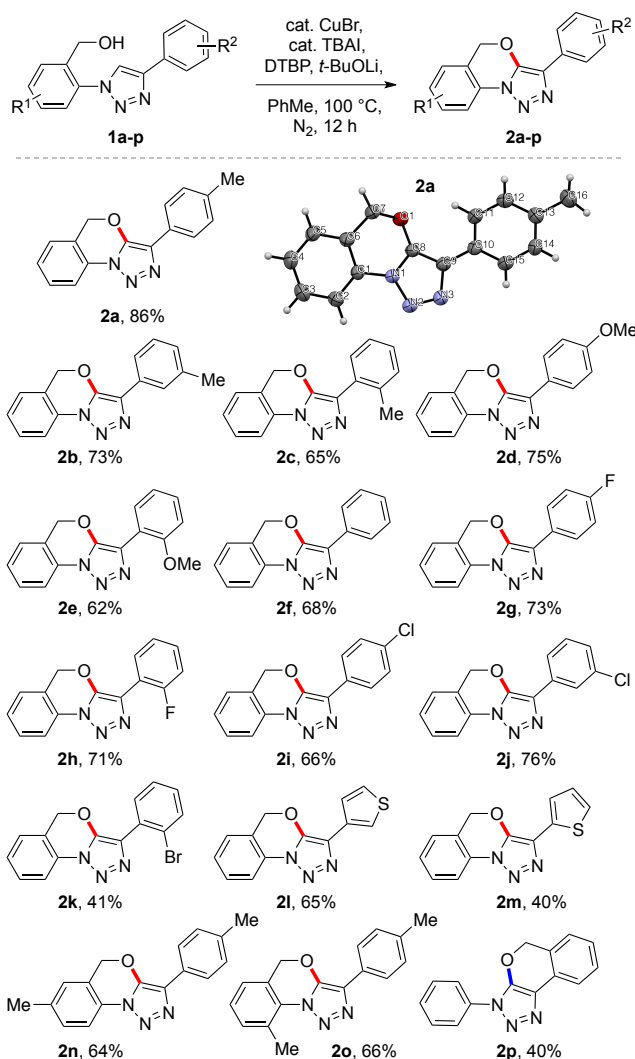
entry	[Cu]	Base	Oxidant	Solvent	Temp (°C)	Yield <sup>b</sup> (%)
1	CuBr	<i>t</i> -BuOLi	DTBP	DCE	120	53
2	CuBr	<i>t</i> -BuOLi	BAIB	DCE	120	<5
3	CuBr	<i>t</i> -BuOLi	TBHP	DCE	120	13
4	CuBr	<i>t</i> -BuOLi	DTBP	THF	120	35
5	CuBr	<i>t</i> -BuOLi	DTBP	PhCF <sub>3</sub>	120	45
6	CuBr	<i>t</i> -BuOLi	DTBP	PhCH <sub>3</sub>	120	57
7	CuBr	<i>t</i> -BuOK	DTBP	PhCH <sub>3</sub>	120	33
8	CuBr	<i>t</i> -BuONa	DTBP	PhCH <sub>3</sub>	120	27
9	CuBr	AcOLi	DTBP	PhCH <sub>3</sub>	120	17
10	<b>CuBr</b>	<b><i>t</i>-BuOLi</b>	<b>DTBP</b>	<b>PhCH<sub>3</sub></b>	<b>100</b>	<b>86</b>
11	CuBr	<i>t</i> -BuOLi	DTBP	PhCH <sub>3</sub>	80	32
12	CuCl	<i>t</i> -BuOLi	DTBP	PhCH <sub>3</sub>	100	41
13	CuI	<i>t</i> -BuOLi	DTBP	PhCH <sub>3</sub>	100	45
14	Cu(acac) <sub>2</sub>	<i>t</i> -BuOLi	DTBP	PhCH <sub>3</sub>	100	47
15	CuBr	<i>t</i> -BuOLi	–	PhCH <sub>3</sub>	100	26
16	CuBr	–	DTBP	PhCH <sub>3</sub>	100	0
17 <sup>c</sup>	CuBr	<i>t</i> -BuOLi	DTBP	PhCH <sub>3</sub>	100	31
18	–	<i>t</i> -BuOLi	DTBP	PhCH <sub>3</sub>	100	0

<sup>a</sup>Reaction conditions: **1a** (0.3 mmol), copper salt (20 mol %), additive (10 mol %), base (1.2 mmol) and oxidant (0.45 mmol) in solvent (2.0 mL) under N<sub>2</sub> at the stated temperature for 12 h. <sup>b</sup>Isolated yield. <sup>c</sup>Conducted in the absence of TBAI.

modest improvement using toluene (57%, Entries 4–6). Use of other bases (*t*-BuONa, *t*-BuOK, and AcOLi) led to no improvement (Entries 7–9); however, reducing the reaction temperature to 100 °C led to a marked enhancement in yield (86%, Entry 10). These proved to be the optimal conditions, as other copper salts (CuCl, CuI, and Cu(acac)<sub>2</sub>) offered no advantage (Entries 12–14), while the need for CuBr, TBAI, base and oxidant was confirmed through control experiments (Entries 15–18).

With optimized conditions in hand, the scope of the alkoxylation reaction was studied for a range of 1,4-diaryl 1,2,3-triazoles (Figure 1). In general, electron-donating and moderately electron-withdrawing groups were accommodated at various positions on either aromatic ring, furnishing the tricyclic products in good yields (**2a–2o**, 40–86%). While superior results were observed for *para* substituents, it is notable that *ortho* substitution afforded near-equivalent yields (compare **2b/2c** and **2n/2o**), in spite of the increase in steric hindrance. Other noteworthy features are the tolerance of halogen substituents that would enable further product functionalization (such as bromide **2k** and chlorides **2i–j**, 41–76%), and heteroaromatic thiophene sidechains **2l** and **2m**, albeit the yield for the 2-thiophenyl group was lower (40–65%). Finally, the novel isomeric fused triazole **2p** could be formed from insertion of

**Figure 1. Reaction Scope.<sup>a</sup>**



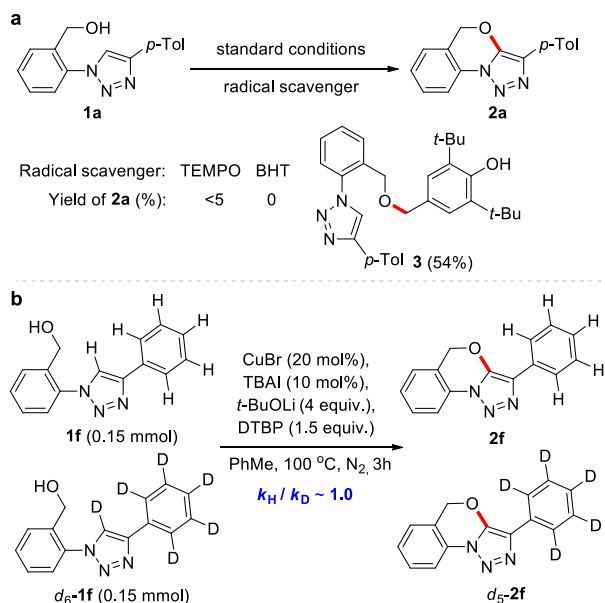
<sup>a</sup>Reaction conditions: **1** (0.3 mmol), copper salt (20 mol %), TBAI (10 mol %), *t*-BuOLi (1.2 mmol), DTBP (0.45 mmol), toluene (2.0 mL), N<sub>2</sub>, 100 °C, 12 h. Yields are isolated yields. Ellipsoids for the single crystal X-ray structure of **2a** are shown at 50% probability.

a benzylic alcohol on the 4-aryl group, rather than 1-aryl.

Two experiments were performed to gain insight into the mechanism of this novel C–H alkoxylation (Scheme 2). Performing the reaction under optimized conditions, but in the presence of TEMPO or BHT, resulted in complete inhibition of the formation of **2a** (Scheme 2a), which suggests that the reaction may indeed proceed through a radical pathway; in addition, a product of alkoxyl radical trapping (**3**) was isolated in 54% yield using BHT as inhibitor. A kinetic isotope effect (*k<sub>H</sub>*/*k<sub>D</sub>*) of ~1.0 was observed for the reaction of **1f** relative to **d<sub>6</sub>-1f** (Scheme 2b), which suggests that C–H/D bond cleavage is not involved in the rate limiting step.

Based on these results and related literature precedent,<sup>16</sup> a possible reaction mechanism is outlined in Scheme 3. First, single-electron oxidation of Cu(I) by DTBP would generate Cu(II), *t*-BuO<sup>•</sup>, and *t*-BuO<sup>–</sup>. Deprotonation of the benzylic alcohol leads to Cu(II)alkoxide **A**, which disproportionates to alkoxide radical **B** and Cu(I) via SET to the metal.<sup>16d</sup> Addition of the alkoxyl radical to the C5 position of the triazole affords carbon-centered radical **C**,

**Scheme 2. a. Radical Inhibition Experiments and b. Kinetic Isotope Effect Study.**

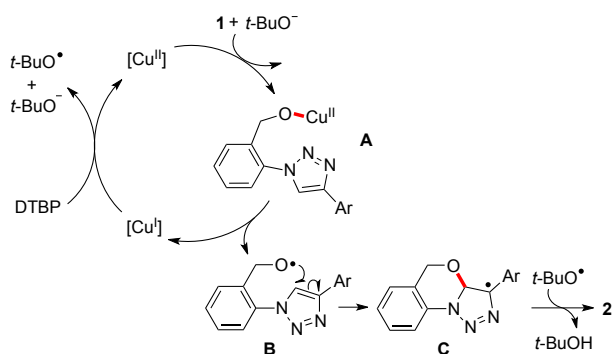


which is transformed to product **2** on reaction with the *tert*-butoxyl radical, or oxidation by Cu(II) followed by aromatization (Scheme 3).<sup>16</sup>

The tricyclic fused ring triazole products **2** have potential utility in medicinal and agrochemistry as novel heterocyclic scaffolds. In light of the known antifungal activity of other triazoles,<sup>12</sup> we evaluated the antifungal properties of **2a–o** against three fungal strains (*F. oxysporum*, *F. solani*, and *C. destructans*), which are the main pathogenic fungi associated with ginseng root-rot disease, using the microbroth dilution technique (Table 2).<sup>17</sup> Pleasingly, several compounds showed promising levels of inhibition of *F. oxysporum* compared to existing antifungal agents. **2c** in particular exhibited excellent activity against all strains. Several compounds (**2e–g**, **2j–2m**) showed good inhibitory activity against *F. oxysporum*, while **2l** also exhibited activity against *C. destructans*. **2n** and **2o** showed selectivity for the latter.

In conclusion, a simple and efficient protocol for the synthesis of tricyclic triazole-benzoxazines *via* copper-catalyzed intramolecular C–H triazole alkoxylation has been developed. To the best of our knowledge, this is the first example of transition metal-catalyzed C5 alkoxylation of the 1,2,3-triazole ring, a heterocycle which is itself commonly regarded as a useful C–H functionalization directing

### Scheme 3. Possible Reaction Mechanism.



**Table 2. Antifungal properties of compounds 2a–2o.<sup>a</sup>**

entry	triazole	<i>F. oxysporum</i>	<i>F. solani</i>	<i>C. destructans</i>
1	<b>2a</b>	150.0±0.0	>150.0	>150.0
2	<b>2b</b>	>150.0	>150.0	>150.0
3	<b>2c</b>	<b>2.1±0.3</b>	<b>94.0±18.8</b>	<b>93.7±18.8</b>
4	<b>2e</b>	<b>9.4±0.0</b>	>150.0	>150.0
5	<b>2f</b>	<b>10.0±2.0</b>	>150.0	>150.0
6	<b>2g</b>	<b>1.2±0.0</b>	>150.0	>150.0
7	<b>2h</b>	>150.0	>150.0	>150.0
8	<b>2i</b>	150±0.0	>150.0	>150.0
9	<b>2j</b>	<b>9.4±0.0</b>	>150.0	>150.0
10	<b>2k</b>	<b>13.1±2.2</b>	>150.0	>150.0
11	<b>2l</b>	<b>37.5±0.0</b>	150.0±0.0	<b>65.6±9.4</b>
12	<b>2m</b>	<b>3.3±0.6</b>	>150.0	>150.0
13	<b>2n</b>	150.0±0.0	>150.0	<b>37.3±0.0</b>
14	<b>2o</b>	>150.0	>150.0	<b>23.4±4.7</b>
15 <sup>b</sup>	Hymexazol	50.0±13.0	12.5±3.1	12.5±3.1
16 <sup>b</sup>	Flutriafol	37.5±0.0	135.0±15.0	3.8±0.6
17 <sup>b</sup>	Grondverbeteraar	>150.0	>150.0	75.0±0.0
18 <sup>b</sup>	Propamocarb	150.0±0.0	>150.0	150.0±0.0

<sup>a</sup>MIC values are given in  $\mu\text{g/mL}$ . <sup>b</sup>Positive controls.

group. These tricyclic structures show potential as novel scaffolds in medicinal chemistry, here evidenced by their marked antifungal activity against *F. oxysporum*, *F. solani*, and *C. destructans*, the causal pathogens of ginseng root-rot disease.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, mechanistic studies, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra (PDF) and crystallographic data (CIF).

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### Notes

The authors declare no competing financial interest.

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## TOC entry:

