C–H Bond Activation

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Copper as a Powerful Catalyst in the Direct Alkynylation of Azoles**

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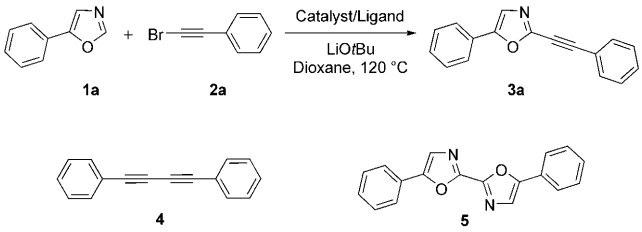
The widespread use of heteroarenes in medicinal chemistry and in materials science has driven the development of a plethora of new synthetic strategies to prepare appropriately substituted heterocyclic cores. In particular, transition-metal-catalyzed direct functionalization has gained enormous attention over the past decade as an effective and straightforward method for creating aryl/alkenyl–heteroaryl linkages because it presents many advantages over traditional cross-coupling reactions.[1] Clearly, major time and atom economies can be achieved once the need to prepare a suitably activated heteroarene has been eliminated. A wide range of metal catalysts, including palladium, rhodium, and ruthenium, and to a lesser extent copper and nickel, have been exploited for these processes, providing a toolbox of tunable reaction conditions for a large range of substrates.[2,3] However, one key reaction remains largely unexplored, namely the creation of an alkynyl–heteroaryl linkage between an sp^2-hybridized heteroaryl carbon and an sp-hybridized carbon of an alkynyl halide using C–H bond activation.[4]

The few known examples of direct alkynylation deal principally with benzene derivatives bearing an *ortho* directing group, using gallium salts as the catalyst and silylated haloethynes as the coupling partner.[5] Recently, two notable exceptions were reported by Gevorgyan and later by Gu and Wang in which two classes of electron-rich heterocycles were alkynylated using various bromoalkynes.[6] In the former case, high dilution conditions were required, whilst the latter case was limited by substrate scope. Given that these two methods rely on the use of palladium catalysis, we decided to explore the development of an efficient, general, copper-catalyzed procedure for the direct alkynylation of various heterocycles that exploits the minimal cost and toxicity of copper.

To test this possibility, and based on our previous work on heteroarene direct alkenylation, we began with the reaction between 5-phenyloxazole (**1a**) and bromophenylacetylene (**2a**). We screened a series of copper/ligand sources, beginning with CuI/*trans*-*N*,*N*′-dimethyl ethylene-1,2-diamine (dmeda); LiO*t*Bu was added as base and the mixture was heated in dioxane to 120 °C (Table 1, entry 1).[3b,7] Unfortunately, the only isolated product was the symmetrical diyne (**4**) resulting from the rapid homocoupling of the alkynylbromide through an Ullmann-type reaction. A satisfactory result was obtained when dipivaloylmethane (dpm) was used as ligand instead of dmeda to afford the alkynyloxazole (**3a**) in 43% yield (Table 1, entry 3).

A subsequent screen of copper sources, using dpm as the ligand, gave only modest improvement of the yield; the best result was achieved with $Cu(OTf)_2$, although conversion was still incomplete (Table 1, entries 3–7). A drastic improvement was observed by switching to phosphine ligands (Table 1, entries 8–13), with the highest yield (89%) obtained using bis[(2-diphenylphosphino)phenyl] ether (DPEPhos) in combination with $CuBr{\cdot}SMe_2$ after only 1 h (Table 1, entry 13).[8] Interestingly, the use of uncomplexed CuBr led to a decrease in the yield of **3a** (70%; Table 1, entry 14) and enhanced

Table 1: Optimization of the direct alkynylation reaction of 5-phenyloxazole.[a]



1a **2a** **3a**

4

5

Entry	Catalyst (mol%)	Ligand (20 mol%)	*t* [h]	Yield [%][b]
1	CuI (15)	dmeda	24 h	–
2	CuI (15)	1,10-phen	24 h	–
3	CuI (15)	dpm	7 h	43
4	CuBr (15)	dpm	4 h	–
5	$Cu(OTf)_2$ (5)	dpm	3 h	56
6	$CuSO_4{\cdot}5\,H_2O$ (10)	dpm	24 h	22
7	$Cu(OAc)_2$ (10)	dpm	5 h	15
8	$Cu(OTf)_2$ (15)	PPh_3	3 h	64[c]
9	$Cu(OTf)_2$ (15)	P(*t*Bu)$_3$	3 h	–
10	$Cu(OTf)_2$ (10)	DPEPhos	5 h	57
11	CuI (10)	PPh_3	1 h	71
12	$CuBr{\cdot}SMe_2$ (10)	PPh_3	2 h	69
13	$CuBr{\cdot}SMe_2$ (10)	DPEPhos	1 h	89
14	CuBr (10)	DPEPhos	2 h	70
15	$CuBr{\cdot}SMe_2$ (10)	–	2 h	24
16	$Pd(PPh_3)_4$	–	24	< 5
17	$PdCl_2(PPh_3)_2$	–	4 h	–[d]
18	$Pd(PPh_3)_4$/CuI	–	24 h	–[e]

[a] All reactions were performed using 0.35 M of 5-phenyloxazole **1a** (1 equiv), 1-bromophenylacetylene **2a** (2 equiv) and LiO*t*Bu (2 equiv) in dioxane at 120 °C. [b] Yields are calculated from isolated products. [c] 58% for 15 h. [d] KOAc and toluene were used (Gevorgyan conditions). [e] Cs_2CO_3 used as base, and *N*,*N*-dimethyl formamide as solvent; 150 °C.

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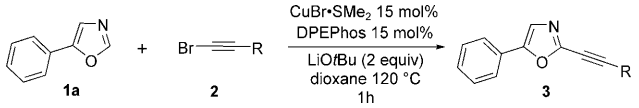
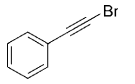
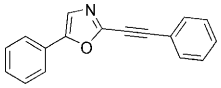
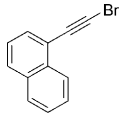
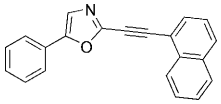
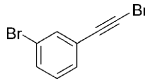
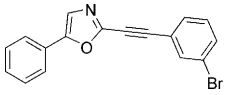
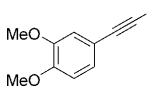
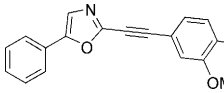
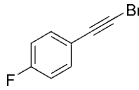
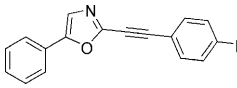
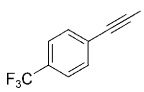
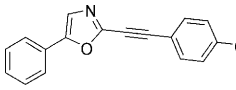
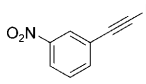
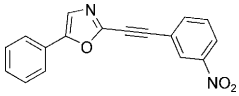
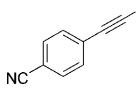
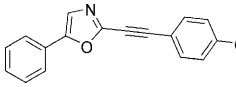
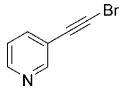
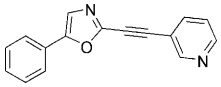
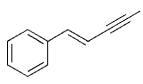
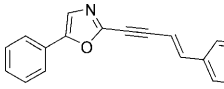
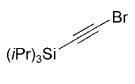
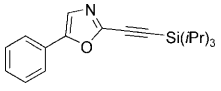
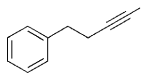
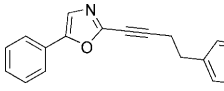
formation of the by-product 5-phenyloxazole dimer **5** (5% to 30%). In the absence of DPEPhos, a lower conversion into product **3a** (24%) and increased yield of the homocoupling product **5** was observed (42%, Table 1, entry 15). Clearly, CuBr alone is still able to catalyze the formation of **5**, and so to prevent this unwanted side reaction, rapid generation of the CuBr/DPEPhos species is required. The greater success of the copper bromide/dimethyl sulfide complex lies in the increased solubility over the uncomplexed copper bromide, which makes it available immediately for coordination in the reaction medium. A brief survey of bases was therefore undertaken in which optimal results were achieved using LiO*t*Bu, with weaker bases (K_2CO_3, Cs_2CO_3, and K_3PO_4) resulting in no product formation. 1,4-Dioxane was found to be the preferred solvent, as reactions in *N*,*N*-dimethyl formamide or acetonitrile resulted in no conversion into the product **3a**. Palladium catalysts were also tested but, in contrast to the copper system, these were found to be ineffective. Therefore, we identified CuBr·SMe_2 (15 mol%)/DPEPhos (15 mol%)/LiO*t*Bu (2 equiv)/dioxane/120°C as the best conditions for the coupling of 5-phenyloxazole with bromoalkyne; product **3a** was synthesized in 1 h and in 89% yield.

Table 2: Scope of direct alkynylation of 5-phenyloxazole with alkynyl bromides.[a]



Entry	Alkynyl bromide	Product	Yield [%][b]
1			**3a** 89 (81)[c]
2			**3b** 84
3			**3c** 74
4			**3d** 82
5			**3e** 89
6			**3f** 76
7			**3g** 73
8			**3h** 66
9			**3i** 73
10			**3j** 73
11			**3k** 84
12			**3l** 26

[a] 5-Phenyloxazole (0.35 M, 1 equiv), alkynyl bromide (2 equiv), dioxane, 120°C for 1 h. [b] Yields are calculated based on isolated products. [c] Yield in parentheses is obtained for a reaction performed on a gram-scale.

This optimized procedure was subsequently used to investigate the scope of the direct alkynylation reaction of 5-phenyloxazole using various readily accessible 1-bromoalkynes (Table 2). Two methods are commonly used for their preparation: 1) bromination of terminal alkynes using NBS/$AgNO_3$; or 2) a two-step sequence involving formation of 1,1-dibromoalkenes from their corresponding commercially available aldehydes, followed by a DBU/DMSO-promoted dehydrobromination.[9] Both electron-rich (Table 2, entries 1–5) and electron-deficient (Table 2, entries 6–8) alkynyl bromides reacted regioselectively at the C2 position of **1a** in good yields, with substitution being tolerated at each of the *ortho*, *meta*, and *para* positions. The reaction proceeds equally well with heteroaryl- and alkenyl-susbtituted alkynes (Table 2, entries 9 and 10); however, alkyl-substituted **3l** was obtained in a disappointing 26% yield (Table 2, entry 12). Noteworthy is the (triisopropylsilyl)bromoacetylene, which underwent coupling to afford the silyl-substituted alkynyloxazole **3k** in 84% yield; alkynyloxazole **3k** is a precursor to the versatile terminal acetylene, and has potential for further elaboration (Table 2, entry 11).[10] The C2 regioselectivity of the reaction was in agreement with that reported for the C–H bond functionalization of 5-substituted oxazoles, and was unambiguously confirmed by single-crystal X-ray diffraction analysis of compound **3f**, in which the unit cell was composed of two molecules (Figure 1).[11]

These reaction conditions were also successfully applied to electron-rich and electron-poor oxazoles (Table 3, entries 1 and 2). Remarkably, oxazole itself was regioselectively

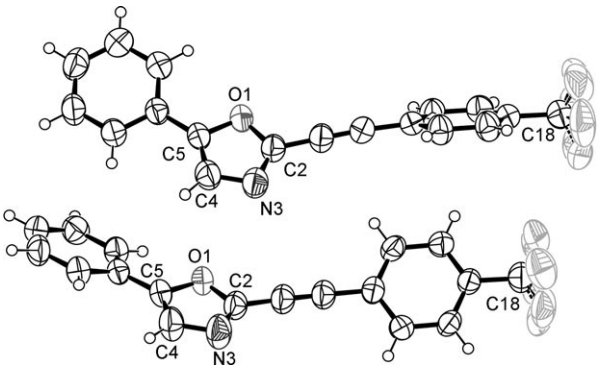
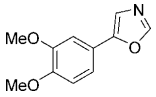
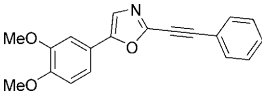
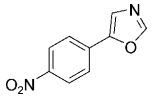
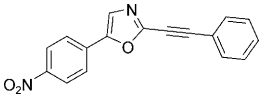
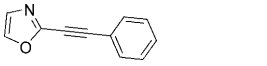
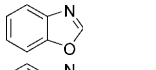
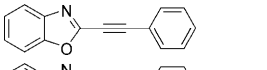
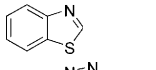
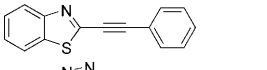
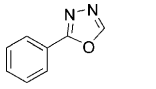
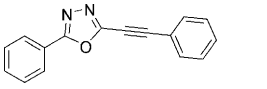
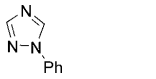
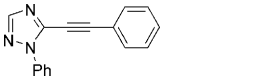
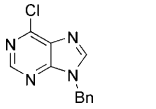
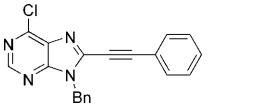


Figure 1. ORTEP of the two independent molecules compound **3f**. Ellipsoids set at 50% probability; the fluorine atoms on C18 are disordered.[12]

Table 3: Testing the scope of the heterocycle substrate.[a]

Entry	Heterocycle	Product		Yield [%][b]
1			**6**	85
2			**7**	92
3			**8**	50
4			**9**	75
5			**10**	90
6			**11**	71
7			**12**	80
8			**13**	50

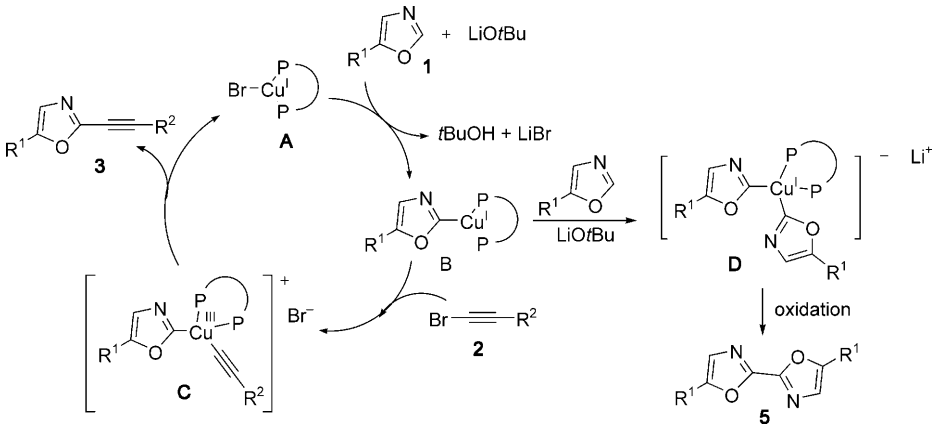
[a] Heterocycle (1 equiv), 2 equiv of phenylacetylene bromide (**2a**), $CuBr{\cdot}SMe_2$ (15 mol%), DPEPhos (15 mol%) and LiO*t*Bu (2 equiv), in dioxane at 120°C for 1 h. [b] Yields are calculated based on isolated products.

alkynylated at the C2 position, albeit in moderate yield (50%; Table 3, entry 3). Other heterocycles, such as benzoxazole, benzothiazole, 1,3,4-oxadiazole, and 1,2,4-triazole were also found to be suitable substrates (Table 3, entries 4–7).

Whilst compounds with higher pK_a values (≥ 30), such as imidazoles, gave mediocre results (not shown), the reaction proceeded in satisfactorily yield with *N*-benzyl-6-chloropurine (50%; Table 3, entry 8). This result is particularly noteworthy as it leaves the C–Cl bond untouched; it therefore allows subsequent functionalization at this position to access biologically interesting 6,8,9-trisubstituted purines.[13]

Although the precise mechanism of this new process is unclear at this stage, the reaction probably proceeds through the formation of a copper(III) complex (**C**; Scheme 1), because such species are commonly speculated as intermediates in the copper-mediated Ullmann reaction and recently in the C–H bond arylation reaction.[14] The sequence begins with deprotonation of the oxazole by LiO*t*Bu, followed by lithium–copper transmetallation to generate copper(I)(oxazolate) intermediate **B**, as illustrated by Do and Daugulis for the copper-catalyzed direct arylation of heterocycles.[15] Oxidative addition of **B** onto the alkynyl bromide presumably gives a four-coordinate copper(III) complex (**C**). Subsequent reductive elimination would lead to the expected alkynylated compound **3**, and regenerate the catalytic copper(I) species **A** in the process. Furthermore, this mechanism rationalizes the beneficial effect of using a bulky chelating ligand (compare Table 1, entries 12 and 13), as it is the DPEPhos, rather than the monodentate triphenylphosphine, that gives a lower conversion into the product (89% and 69% respectively). Indeed, formation of the mixed copper(III)(alkynylate)(oxazolate) intermediate **C** is thought to compete directly with activation of a second equivalent of oxazole, which would afford bis(oxazolate) copper(I) species **D**, and subsequently the undesired bis(oxazole) dimer **5**. However, steric hindrance about the copper center blocks access of the second oxazolate that would generate **D**; the less sterically demanding alkyne enters more freely, thus preferentially forming **C**. Finally, with **B** generated quickly in the reaction medium, thanks to the solubility of the dimethylsulfide complex and a strong preference for the formation of **C** because of the bulky bidentate ligand, the equilibrium is driven toward the formation of the desired product **3**. This C–H alkynylation can be considered as a "reverse Sonogashira" reaction because a) the first organocopper species formed derives from the heterocycle and not from the acetylene, and b) the acetylene, rather than the heterocycle, is involved in the oxidative addition step.

In summary, we have developed new conditions for a C–H bond functionalization that enables the first entirely copper-catalyzed direct alkynylation of heterocycles. This reaction is very rapid, is functional group tolerant, and provides a straightforward entry to diverse alkynyl heterocycles that is complementary to the well-established Sonogashira reaction. This work illustrates once again that inexpensive copper salts are able to supplement palladium catalysis in the field of C–H bond activation.



Scheme 1. Mechanistic proposal for copper-catalyzed direct alkynylation of heterocycles with alkynyl bromides.

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