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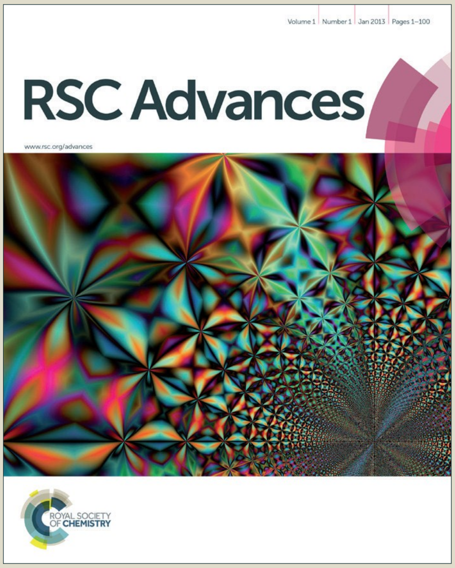

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COMMUNICATION

Regioselective Copper-Diamine-Catalyzed C-H Arylation of 1,2,4-Triazole Ring with Aryl Bromides

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A convenient methodology for the regioselective C-H arylation of 1,2,4-triazole ring was developed. Using a benchtop stable Cu-diamine catalyst system, the C-H functionalization of a simple 1,2,4-triazole substrate with various aryl bromides was regioselectively accomplished at the C5 position of the triazole ring.

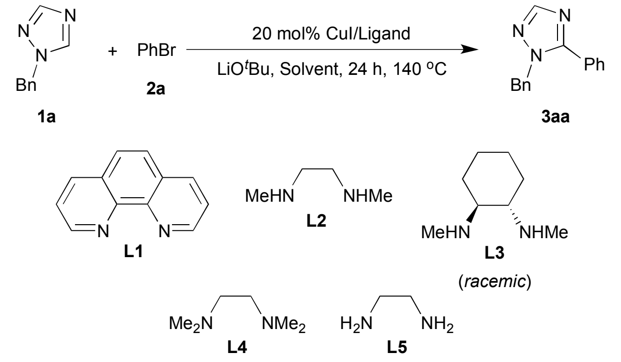
Developments in Cu catalysis have taken a striding step in advancing the science of organic synthesis.[1] Since their renaissance, Cu-catalyzed cross-coupling reactions have been at the realm of various applications for forging the C-heteroatom and C-C bonds. With time, interests in developing the inexpensive and low toxic Cu-catalyzed C-H functionalization methodologies have also been growing.

The methodological evolution leading to the direct C-H arylation of heterocycles is an evidence of the breakthrough in contemporary copper catalysis.[2] This recent development marked the emergence of a sustainable alternative to traditional transition metal catalysis for construction of the privileged heterocycles.[3]

The 1,2,4-triazole is an example of heterocycle with established applications in the medicinal and material chemistries.[4] Daugulis previously demonstrated the Cu-catalyzed direct C5 arylation of 1-methyl-1*H*-1,2,4-triazole with iodobenzene through a regioselective non-benzyne mechanism.[5] However, despite its potential, interest in accomplishing the regioselective C-H arylation of the triazole ring under Cu catalysis remained limited.[6] Therefore, our interest was subsequently extrapolated to the worthwhile endeavors in developing the streamlined regioselective approach towards C5-arylated 1,2,4-triazoles.

Endeavoring on the development of a benchtop stable procedure using easily accessible and inexpensive substrates, the arylation of 1-benzyl-1*H*-1,2,4-triazole **1a** with bromobenzene **2a** was initially investigated. Under the typical reaction conditions consisting of CuI (20 mol%) and LiO^{t}Bu (2.0 equiv.), the anticipated arylation to afford **3aa** was encouraging observed in 40% yield (Table 1, entry 1).

Table 1. Screening of Cu-catalyzed conditions for C-H arylation of **1a** with **2a**.[a]



Entry	Ligand	Solvent	Yield[b]
1	-	Dioxane	40
2	**L1**	Dioxane	50
3	**L2**	Dioxane	62
4	**L3**	Dioxane	27
5	**L4**	Dioxane	41
6	**L5**	Dioxane	36
7	**L2**	Dioxane	53[c]
8	**L2**	Dioxane	45[d]
9	**L2**	Dioxane	55[e]
10	**L2**	DMF	Trace
11	**L2**	^{t}AmylOH	46
12	**L2**	PhMe	48

[a] General reaction conditions: **1a** (0.5 mmol), **2a** (3.0 equiv.), 20 mol% CuI/Ligand, LiO^{t}Bu (2.0 equiv.), Solvent (0.5 mL), 140 °C, 24 h. [b] Isolated yield. [c] **L2** (30 mol%). [d] 10 mol% CuI/**L2**. [e] Reaction temparature of 120 °C.

The reaction also proceeded when 20 mol% 1,10-phenanthroline (**L1**) was added to the reaction system albeit with only a slight improvement in yield (entry 2). Though limited to the arylation of 1-methyl-1*H*-1,2,4-triazole with

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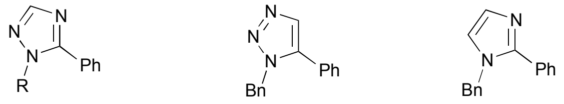
iodobenzene, **L1** was previously speculated to be an effective ligand for stabilizing the organocopper complex and facilitating the halide displacement step.[5] Therefore, with the prescience in the role of a ligand, potential of other ligated Cu-catalyzed systems for the direct arylation of **1a** with **2a** was next considered.

The diamines are an important class of ligands for the successful reemergence of copper catalysis in organic synthesis.[7] Furthermore, the role of a diamine ligand had also been reported in the related Cu-catalyzed C-H alkenylation of oxazoles with bromoalkenes.[8] Hence, we performed a set of screening experiments to assess the potential of several commercially available diamines ligands for our Cu-catalyzed reaction (entry 3 – 6). The best outcome led to a 62% yield of **3aa** when DMEDA (**L2**) was added to the reaction system (entry 3). Notably, in this attempt, no oxidative homocoupling of **1a** was observed unlike in all other attempts whereby traces of the byproduct were observable.[9] Therefore, **L2** was identified as an effective diamine ligand for the Cu-catalyzed coupling of **1a** with **2a** presumably by stabilizing the organocopper complex of **1a** and facilitating bromide displacement from **2a**.

With the optimal 20 mol% CuI/**L2** catalyst system at 140 °C (entries 7 – 9), the effect of solvent was next probed. However, no improvement in yield was realized; with DMF notably afforded only trace yield of **3aa** (entry 10). ^{t}AmylOH which was recently reported to accelerate the activation of imidazole C-H under Ni catalysis was also ineffective (entry 11).[10] Further attempts to circumvent the observed incomplete reaction were also conducted. However, no considerable improvement was achieved with either an extended reaction time or increased catalyst loading. Additionally, other Cu(I) sources (CuBr and CuCl) and bases (K_3PO_4 and K_2CO_3) were significantly ineffective with only a trace of **3aa** was formed in each of these attempts.

With the optimal conditions of Table 1 (entry 3), our studies were next continued by investigating the arylation of other five-membered N-containing heterocycles.[11] Generally, all 1,2,4-triazole substrates tested were arylated at the C5 ring position to give the intended products (**3ba** – **3ea**) in moderate 40% to 50% yields (Scheme 1).


R = ^{n}Bu, **3ba**, 40%
R = *(E)*-styryl, **3ca**, 50%
R = Ph, **3da**, 43%
R = *p*-tolyl, **3ea**, 42%

3fa, 22%

3ga, 24%

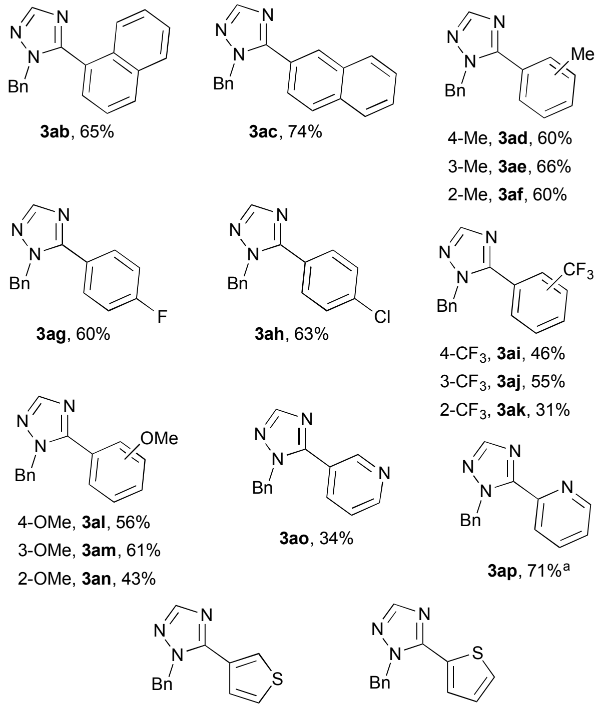
Scheme 1. General reaction conditions: **1b** – **1g** (0.5 mmol), **2a** (3.0 equiv.), 20 mol% CuI/**L2**, LiO^{t}Bu (2.0 equiv.), Dioxane (0.5 mL), 140 °C, 24 h.

The arylation of other simple heterocycles were also attempted. However, with only 22% **3fa** and 24% **3ga**, arylations of the 1,2,3-triazole and imidazole rings were deemed to be markedly inefficient under our general reaction conditions. Pyrazole substrate was also not suitable whereby only the starting material was recovered.

Nonetheless, all arylations occurred regioselectively at the natural reactive sites as dictated by the electronic characters of the heterocycles.[6b,12] Further consideration on the electronic characters could also rationalize the observed differences in reactivities. Generally, with an extra nitrogen atom, the triazole ring could be reasoned to be more electron deficient than either the imidazole or pyrazole ring. This nature of the ring makes it more reactive to undergo the deprotonation step at the predicted reactive C5 position. Hence, better yields were observed in the attempts with 1,2,4-triazole substrates than substrates based on the imidazole and pyrazole rings.

Besides the natural electronic characters, Cu coordination to the heterocyclic substrates could also greatly assist the deprotonation step.[13] This could rationalize the obvious difference in the reactivity between 1,2,4- and 1,2,3-triazoles. In both triazoles, the reactive or acidic C-H bonds occur at the C5 ring position. Therefore, in 1,2,4-triazoles, Cu coordination to the N4 position of the ring could affect a more pronounce acidity enhancement to the adjacent C-H bond at the C5 position and hence facilitate its deprotonation.

With **1a** as the optimal substrate, studies on the arylation with various aryl bromides were next performed (Scheme 2).


3ab, 65%

3ac, 74%

4-Me, **3ad**, 60%
3-Me, **3ae**, 66%
2-Me, **3af**, 60%

3ag, 60%

3ah, 63%

4-CF$_3$, **3ai**, 46%
3-CF$_3$, **3aj**, 55%
2-CF$_3$, **3ak**, 31%

4-OMe, **3al**, 56%
3-OMe, **3am**, 61%
2-OMe, **3an**, 43%

3ao, 34%

3ap, 71%[a]

3aq, 45%

3ar, 56%

Scheme 2. General reaction conditions: **1a** (0.5 mmol), **2b** – **2r** (3.0 equiv.), 20 mol% CuI/**L2**, LiO^{t}Bu (2.0 equiv.), Dioxane (0.5 mL), 140 °C, 24 h. [a]Reaction was conducted under ligand-free conditions.

Our arylation attempts were started with 1- and 2-bromonaphthalene which unambiguously gave the respective

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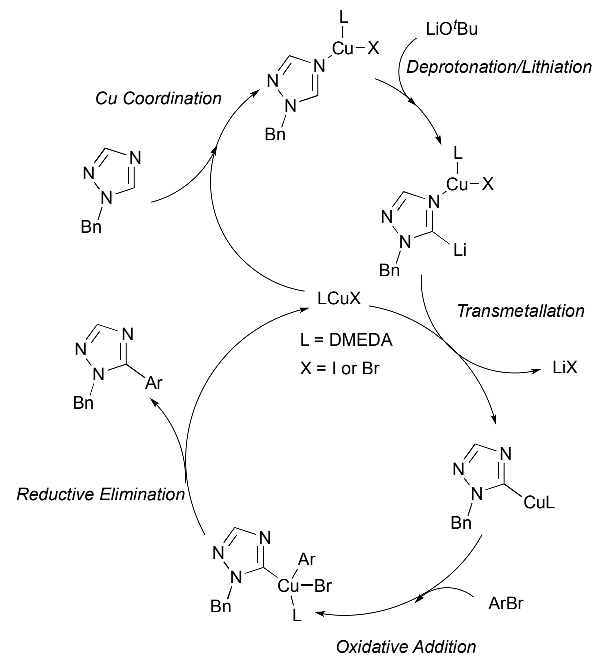
3ab and **3ac** in 65% and 74% yield. With the series of bromotoluenes, **1a** was also accordingly arylated to **3ad**, **3ae** and **3af** in good generality with nearly consistent yields (60%, 66% and 60%). Additionally, a good compatibility of F and Cl substituents on the arylating reagents was also observed whereby **1a** was exclusively arylated to give 60% **3ag** and 63% **3ah**.

However, with electron poor aryl bromides, lower arylation efficiencies were observed. Generally, the regioselective arylations with 4-, 3- and 2-CF_3-substituted bromobenzenes only afforded **3ai**, **3aj** and **3ak** in 46%, 55% and 31% yields respectively. Analogous arylations with the electron rich bromoanisoles were also conducted from which yields of **3al**, **3am** and **3an** were obtained in the range between 43% and 61%. Noticeably, unlike the formation of **3af** from 2-bromotoluene, formations of **3ak** and **3an** could also be influenced by steric factor on the 2-substituted aryl bromides.

Next, the heteroarylation of **1a** was also initiated which afforded **3ao** in only 34% yield from the reaction with 3-bromopyridine. Contrastingly, in the ligand-free reaction with 2-bromopyridine, an exceptionally reactive heteroarylation of **1a** was nonetheless observed whereby up to 71% yield of **3ap** could be obtained. Further attempts to heteroarylate **1a** with bromothiophenes were also carried out. Without any modification to the general Cu-catalyzed conditions, both **3aq** and **3ar** were obtained in 45% and 56% yields respectively.

Apparently, a reaction mechanism involving benzyne intermediate generated from the arylating reagents could be ruled out since only single regioisomers were observed in all cases. Therefore, a plausible reaction mechanism based on the generally accepted mechanistic rationale of Daugulis could be operational to sufficiently account for our observations (Scheme 3).[2b,5]

Generally, the regioselective C-H arylation was firstly initiated by the *tert*-butoxide deprotonation at the C5 position of the 1,2,4-triazole ring. This process necessarily involved the assistance from Cu coordination to N4 position of the ring to ultimately affect a C5 lithiation step. Upon a Li-Cu transmetallation step, a copper complex of 1,2,4-triazole was next generated. Under the assisting influence of the diamine ligand, this reactive organocopper complex would then participate in the coupling with an aryl bromide. For this coupling step, a catalytic cycle involving Cu(I)/Cu(III) intermediates might be proposed to sufficiently describe a sequence of oxidative addition and reductive elimination steps to afford the arylated 1,2,4-triazole product and regenerate the Cu(I) catalyst.



Scheme 3. Plausible reaction mechanism.

In conclusion, an operationally simple Cu-catalyzed protocol for the regioselective C-H arylation of 1,2,4-triazole ring was successfully demonstrated. With a benchtop Cu-diamine catalysis, the regioselective C-H arylation at the C5 ring position of a simple 1,2,4-triazole substrate was conveniently accomplished with various aryl bromides including several heteroaryl bromides. Further efforts to develop similarly simple but more reactive protocol with a wider substrate scope are currently ongoing in our laboratory.

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Regioselective Copper-Diamine-Catalyzed C-H Arylation of 1,2,4-Triazole Ring with Aryl Bromides

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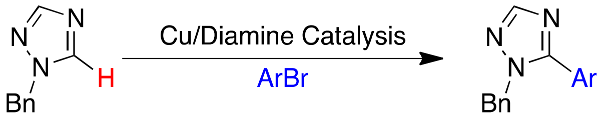
Graphical Abstract



A bench-top protocol using simple Cu-diamine catalysis for the regioselective C5-H arylation of 1,2,4-triazole ring with (hetero)aryl bromides.

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