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Copper-Catalyzed Arylation of Heterocycle C-H Bonds

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Because many pharmaceuticals contain heterocycle-aryl linkages, arylation of heterocycles has received significant attention in the recent years.¹ The shortest and most efficient routes to these compounds involve direct functionalization of heterocycle C-H bonds.² In general, most efforts in cross-coupling methodologies currently are geared toward the replacement of aryl iodides with cheaper aryl chlorides.³ However, for realistic catalyst loadings it is more cost-efficient to replace the expensive transition metal catalyst, usually palladium or rhodium, with a cheaper one.⁴ Use of copper catalysts for the amination and Stille or Suzuki-type couplings has been demonstrated.⁵ Copper-catalyzed direct heterocycle C-H arylation reactions are unknown.^{6,7} We report here a general method for the copper-catalyzed heterocycle arylation by aryl iodides. In addition to electron-rich five membered heterocycles, electron-deficient pyridine oxides can also be arylated. Preliminary mechanistic studies of the arylation are also reported.

Our attention was drawn to the observation that copper salts can affect the regioselectivity of palladium-catalyzed electron-rich heterocycle arylation. Pioneering work in this field was performed by Miura and coworkers who demonstrated that N-methylimidazole is arylated in 2-position if a combination of catalytic Pd and stoichiometric Cu is used, and in 5-position if catalytic Pd is used.⁷ This effect may arise from the involvement of organocopper intermediates in the reaction. If the presumed intermediate could be generated without a palladium cocatalyst, a cheap and efficient method for the heterocycle arylation would be achieved. The organocopper species could be generated by using a stronger base instead of the commonly used cesium or potassium carbonates. Several amide and alkoxide bases were screened in the phenylation of benzoxazole. The best results were obtained by using lithium or potassium *t*-butoxides (Table 1), with LiOtBu/aryl iodide combination affording the highest yields. Equally good results can be obtained in DMF, DMA, DMPU or toluene-DMF mixtures. Commercial, non-anhydrous DMF can be used in all reactions.

The scope with respect to aryl iodide is presented in Table 2. The arylation of benzoxazole shows that electron deficient (entries 1-2) as well as electron-rich (entries 3-7) aryl iodides are reactive. Substantial steric hindrance is tolerated on the aryl iodide (entries 5 and 6). Heteroaryl iodides are also reactive (entry 8). Yields are uniformly excellent, with the exception of mesityl iodide (entry 6).

The scope with respect to the heterocycles is presented in Table 3. Oxazole can be monoarylated in 59% yield, with 7% of the diarylated product isolated (entry 1). 1,3-Thiazole is diarylated in 59% yield (entry 2). 4,5-Dimethylthiazole and benzothiazole are also reactive (entries 3 and 4). 1,2,4-Triazole, benzimidazole, and caffeine are arylated in good yields (entries 5, 6 and 7). Interestingly, electron-deficient 2-phenylpyridine oxide is arylated in 6-position in a 70% yield.⁸ 2-Phenylpyridine and N-methylindole were found to be unreactive under these reaction

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Supporting Information Available: Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

conditions. In most cases, LiOtBu affords the best yields. However, in the case of imidazole or triazole derivatives (entries 5, 6, and 7) use of KOtBu or KOtBu/LiOtBu mixture as a base afforded higher yields.

We have carried out preliminary mechanistic investigations of the coupling process (Scheme 1). The arylation employing KOtBu base is successful for aryl iodides, bromides and chlorides, although the yields are moderate. If 4,5-dimethylthiazole is reacted with iodo- or bromobenzene- d_5 using KOtBu as a base (Scheme 1A), tetradeuterated product **1-1** is obtained. A single hydrogen is introduced at the *ortho*-position of the phenyl group. This observation can be explained by assuming that the reaction proceeds via a copper-assisted benzyne-type mechanism.^{9,10} No H-D exchange is observed if pentadeuterated **1-2** is submitted to the reaction conditions of Scheme 1A. If LiOtBu is used as a base, hydrogen incorporation is not observed (Scheme 1B, **1-2**). Involvement of benzyne intermediate is unlikely in this case. Presumably heterocycle deprotonation by *t*-butoxide (perhaps assisted by copper precoordination to the heterocycle)^{2h} followed by lithium-copper transmetalation and reaction of the organocopper species with aryl iodide leads to the arylation product. No product (LiOtBu base; PhI) or only a trace of the product (<2%; KOtBu base; PhI) was obtained if CuI was omitted from the reaction of Scheme 1.

In conclusion, a new method for the direct, copper-catalyzed arylation of heterocycle C-H bonds by aryl halides has been developed. In addition to electron-rich five-membered heterocycles, electron-poor pyridine oxides can also be arylated. The best results are obtained by using a combination of lithium *t*-butoxide base and aryl iodide coupling partner. The generality and ready availability of starting materials should make this method useful for organic synthesis.

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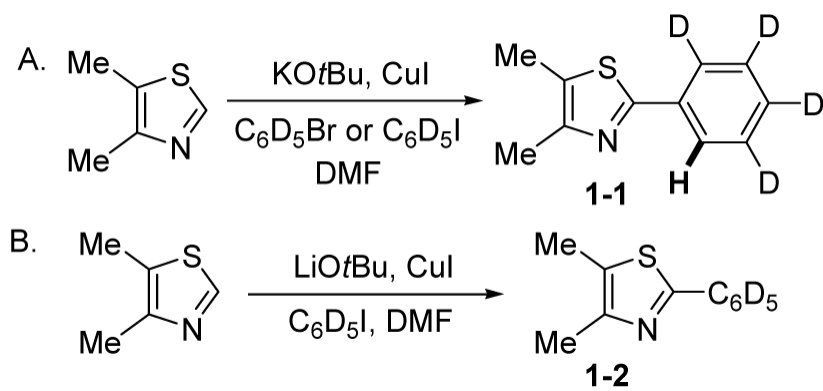
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- The following is the cost breakdown of a molar scale reaction run with three equiv of aryl halide and 5 mol% of palladium acetate or 10 mol% of copper iodide catalyst. The cost of palladium-catalyzed

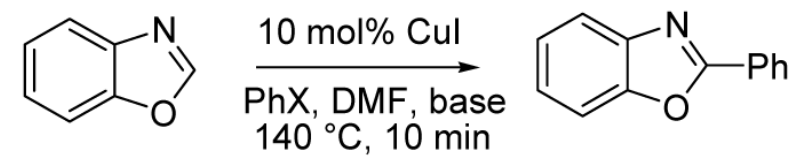
reaction is \$11 (chlorobenzene) + \$403 (Pd(OAc)₂). The cost of copper-catalyzed reaction is \$150 (iodobenzene) + \$3 (CuI; Aldrich prices). An expensive ligand is usually used for palladium-catalyzed reactions.

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10. Arylation of 4,5-dimethylthiazole by *p*-tolyl bromide under conditions of Scheme 1A affords a mixture of *m*-tolyl- and *p*-tolyl derivatives. See Supplementary information for details.



Scheme 1.
Mechanistic investigations.

Table 1

Optimization of the arylation conditions^a

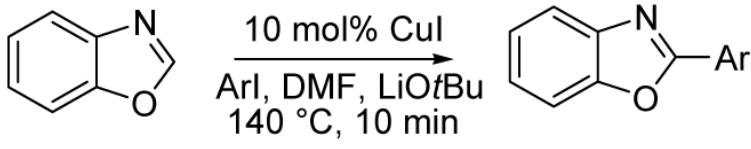
Entry	Base	PhX	Yield, %
1	KOrBu	PhF or PhOTs	No arylation
2 ^b	KorBu	PhCl	40
3	KorBu	PhBr	51
4	KorBu	PhI	61
5	LiOrBu	PhCl, PhBr or PhOTs	No arylation
6	LiOrBu	PhI	93

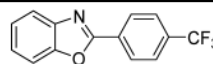
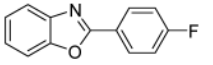
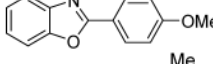
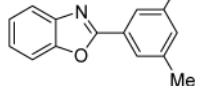
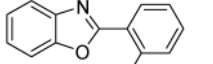
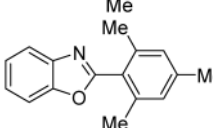
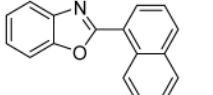
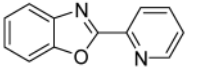
^a Substrate (1 equiv), aryl halide (3 equiv), base (2 equiv). Yields are isolated yields.

^b PhCl (4 equiv), base (3 equiv).

Table 2

Arylation scope with respect to aryl iodides^a


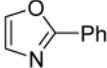

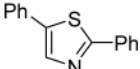

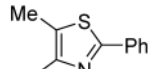

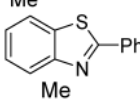

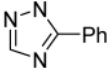
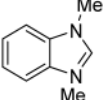
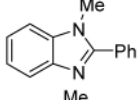
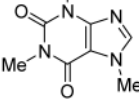
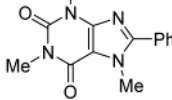

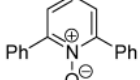


Entry	ArI	Product	Yield, %
1	4-CF ₃ C ₆ H ₄ I		91
2	4-FC ₆ H ₄ I		90
3	4-MeOC ₆ H ₄ I		80
4	3,5-Me ₂ C ₆ H ₃ I		85
5	2-MeC ₆ H ₄ I		91
6	2,4,6-Me ₃ C ₆ H ₂ I		55
7	1-Iodonaphthalene		90
8	2-Iodopyridine		89

^aSubstrate (1 equiv), aryl iodide (3 equiv), base (2 equiv). Yields are isolated yields.

Table 3

Arylation scope with respect to heterocycles^a

Heterocycle		10 mol% CuI	Product	
		PhI, DMF, LiOtBu 140 °C, 10-30 min		
Entry	Heterocycle		Product	Yield, %
1 ^b				59
2 ^c				59
3				84
4				82
5 ^d				57
6 ^e				89
7 ^d				78
8				70

^aSubstrate (1 equiv), iodobenzene (3 equiv), base (2 equiv). Yields are isolated yields.^b2,5-Diphenyloxazole also isolated (7%).^c2-Phenylthiazole also isolated (37%).^dKOtBu base.^eLiOtBu/KOtBu base (1:1).