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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 Stilleor 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 LiO*t*Bu/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 Nmethylindole 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, LiO*t*Bu affords the best yields. However, in the case of imidazole or triazole derivatives (entries 5, 6, and 7) use of KO*t*Bu or KO*t*Bu/LiO*t*Bu mixture as a base afforded higher yields.

We have carried out preliminary mechanistic investigations of the coupling process (Scheme 1). The arylation employing KO*t*Bu 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 KO*t*Bu 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 LiO*t*Bu 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 transmetallation and reaction of the organocopper species with aryl iodide leads to the arylation product. No product (LiO*t*Bu base; PhI) or only a trace of the product (<2%; KO*t*Bu 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 stating materials should make this method useful for organic synthesis.

ACKNOWLEDGMENTS

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REFERENCES

1 (a). Dalvie DK, Kalgutkar AS, Khojasteh-Bakht SC, Obach RS, O'Donnell JP. Chem. Res. Toxicol 2002;15:269. [PubMed: 11896674] (b) Alberico D, Scott ME, Lautens M. Chem. Rev 2007;107:174. [PubMed: 17212475]

2 (a). Akita Y, Inoue A, Yamamoto K, Ohta A, Kurihara T, Shimizu M. Heterocycles 1985;23:2327. (b) Park C-H, Ryabova V, Seregin IV, Sromek AW, Gevorgyan V. Org. Lett 2004;6:1159. [PubMed: 15040747] (c) Yokooji A, Okazawa T, Satoh T, Miura M, Nomura M. Tetrahedron 2003;59:5685. (d) Rieth RD, Mankad NP, Calimano E, Sadighi JP. Org. Lett 2004;6:3981. [PubMed: 15496079] (e) Bellina F, Cauteruccio S, Mannina L, Rossi R, Viel S. J. Org. Chem 2005;70:3997. [PubMed: 15876088] (f) Deprez NR, Kalyani D, Krause A, Sanford MS. J. Am. Chem. Soc 2006;128:4972. [PubMed: 16608329] (g) Okazawa T, Satoh T, Miura M, Nomura M. J. Am. Chem. Soc 2002;124:5286. [PubMed: 11996567] (h) Bellina F, Cauteruccio S, Rossi R. Eur. J. Org. Chem 2006:1379. (i) Bowie AL Jr. Hughes CC, Trauner D. Org. Lett 2005;7:5207. [PubMed: 16268539] (j) Lewis JC, Wu JY, Bergman RG, Ellman JA. Angew. Chem., Int. Ed 2006;45:1589. (k) Chiong HA, Daugulis O. Org. Lett 2007;9:1449. [PubMed: 17358073] (l) Lu J, Tan X, Chen C. J. Am. Chem. Soc 2007;129:7768. [PubMed: 17539649] (m) Stuart DR, Fagnou K. Science 2007;316:1172. [PubMed: 17525334] (n) Wang X, Lane BS, Sames D. J. Am. Chem. Soc 2005;127:4996. [PubMed: 15810815] (o) Dwight TA, Rue NR, Charyk D, Josselyn R, DeBoef B. Org. Lett 2007;9:3137. [PubMed: 17616203] Review: (p) Seregin IV, Gevorgyan V. Chem. Soc. Rev 2007;36:1173. [PubMed: 17576484]

3. Review: Littke AF, Fu GC. Angew. Chem., Int. Ed 2002;41:4177.

4. 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.

5 (a). Klapars A, Antilla JC, Huang X, Buchwald SL. J. Am. Chem. Soc 2001;123:7727. [PubMed: 11481007] (b) Allred GD, Liebeskind LS. J. Am. Chem. Soc 1996;118:2748. (c) Thathagar MB, Beckers J, Rothenberg G. J. Am. Chem. Soc 2002;124:11858. [PubMed: 12358523] (d) Ma D, Liu F. Chem. Comm 2004:1934. [PubMed: 15340608]

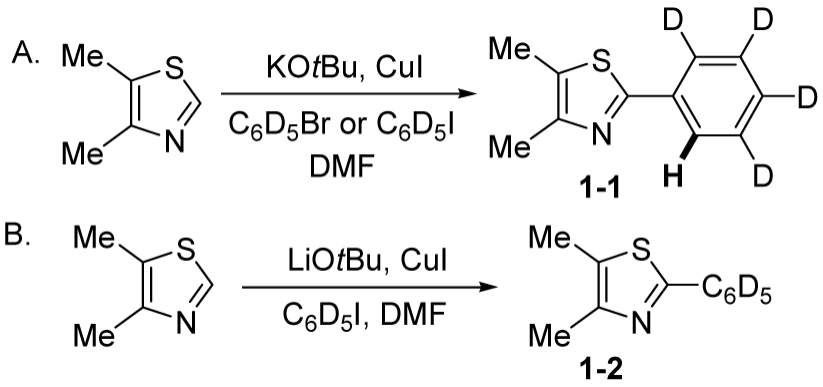
6 (a). Cu-catalyzed oxidation of C-H bonds in 2-phenylpyridines:(a) Chen X, Hao X-S, Goodhue CE, Yu J-Q. J. Am. Chem. Soc 2006;128:6790. [PubMed: 16719450] (b) Uemura T, Imoto S, Chatani N. Chem. Lett 2006;35:842. Cu-catalyzed reaction of indoles with tetrahydroisoquinolines: (b) Li Z, Li C-J. J. Am. Chem. Soc 2005;127:6968. [PubMed: 15884937]

7 (c). Heterocycle arylation under Pd, Pd/Cu catalysis or by using several equiv Cu: Pivsa-Art S, Satoh T, Kawamura Y, Miura M, Nomura M. Bull.Chem. Soc. Jpn 1998;71:467.

8. Palladium-catalyzed pyridine oxide arylation: Campeau L-C, Rousseaux S, Fagnou K. J. Am. Chem. Soc 2005;127:18020. [PubMed: 16366550]

9 (a). Silver-benzyne complex reactions with arene nucleophiles: (a) Friedman L. J. Am. Chem. Soc 1967;89:3071. Review about Cu-catalyzed nucleophilic substitution: (b) Lindley J. Tetrahedron 1984;40:1433. Aryne substitution: (c) Pellissier H, Santelli M. Tetrahedron 2003;59:701. Benzyne reactions with Pd species: (d) Liu Z, Larock RC. J. Org. Chem 72:2007, 223.

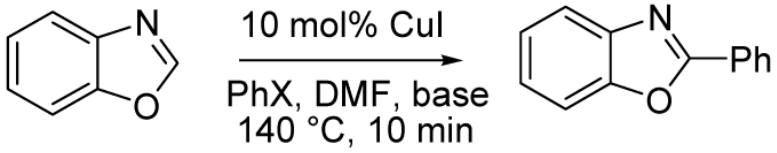
10. Arylation of 4,5-dimethylthiazole by *p*-tolyl bromide under conditions of Scheme 1A affords a mixture of *m*-tolyl- and *p*-tolylderivatives. See Supplementary information for details.



Scheme 1.
Mechanistic investigations.

Table 1

Optimization of the arylation conditions[a]



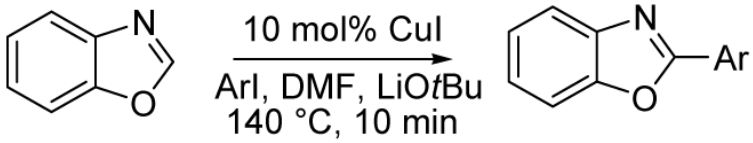
Entry	Base	PhX	Yield, %
1	KO*t*Bu	PhF or PhOTs	No arylation
2[b]	K*ot*Bu	PhCl	40
3	K*ot*Bu	PhBr	51
4	K*ot*Bu	PhI	61
5	LiO*t*Bu	PhCl, PhBr or PhOTs	No arylation
6	LiO*t*Bu	PhI	93

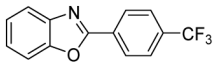
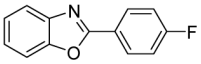
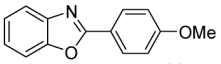
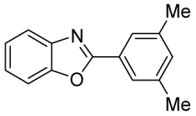
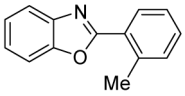
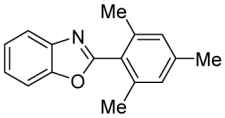
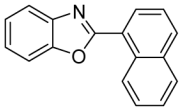
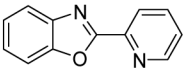
[a] Substrate (1 equiv), aryl halide (3 equiv), base (2 equiv). Yields are isolated yields.

[b] PhCl (4 equiv), base (3 equiv).

Table 2

Arylation scope with respect to aryl iodides[a]

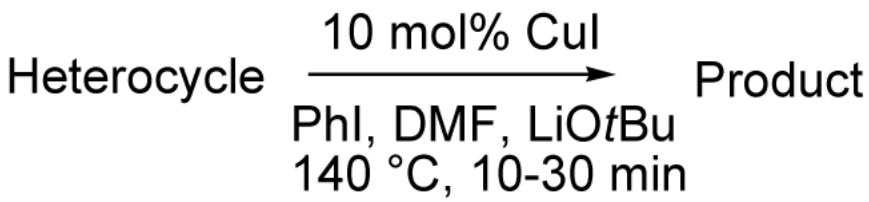


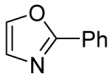
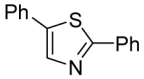
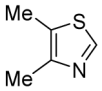
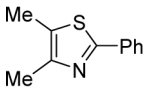
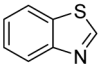
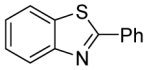
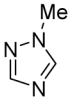
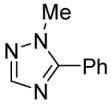
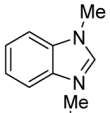
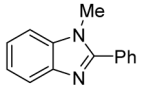
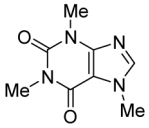
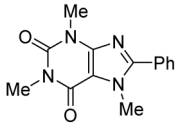
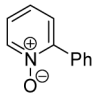
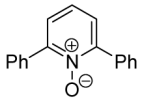
Entry	ArI	Product	Yield, %
1	4-$CF_3C_6H_4I$		91
2	4-FC_6H_4I		90
3	4-$MeOC_6H_4I$		80
4	3,5-$Me_2C_6H_3I$		85
5	2-MeC_6H_4I		91
6	2,4,6-$Me_3C_6H_2I$		55
7	1-Iodonaphthalene		90
8	2-Iodopyridine		89

[a]Substrate (1 equiv), aryl iodide (3 equiv), base (2 equiv). Yields are isolated yields.

Table 3

Arylation scope with respect to heterocycles[a]



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

[a] Substrate (1 equiv), iodobenzene (3 equiv), base (2 equiv). Yields are isolated yields.

[b] 2,5-Diphenyloxazole also isolated (7%).

[c] 2-Phenylthiazole also isolated (37%).

[d] KO*t*Bu base.

[e] LiO*t*Bu/KO*t*Bu base (1:1).