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Copper-Catalyzed Coupling of Hydroxylamines with Aryl Iodides

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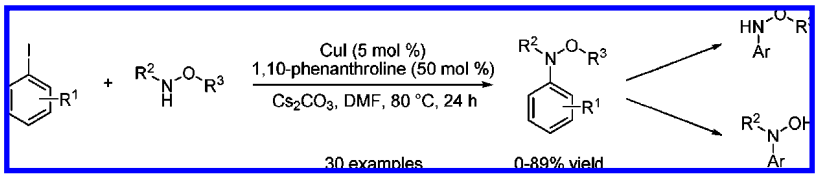
ABSTRACT



An efficient method for the copper-catalyzed *N*-arylation of hydroxylamines with aryl iodides is described. A variety of *N*- and *O*-functionalized hydroxylamines were transformed in good to excellent yield with a broad range of aryl coupling partners. Methods for the selective deprotection of either the *N*- or *O*-substituents for further functionalization are also described.

Over the past decade the copper-catalyzed modified Ullmann condensation of aryl halides with amines has emerged as a powerful and robust bond construction process.[1] The tolerance of a broad spectrum of functionality within both coupling partners has greatly accelerated the up-take of this chemistry worldwide such that the methodology is now an integral part of the organic chemist's toolbox.

With regards to the amine partner a number of methods have been reported for the coupling of primary and secondary amines,[2] anilines,[3] hydrazides,[4] amides,[5] carbamates,[6] amino acids,[7] and imidazoles,[8] among others, showing the outstanding utility of these reactions. Despite the broad spectrum of coupling partners that have been described, we are unaware of any reports of the copper-catalyzed *N*-arylation of hydroxylamines even with the versatility of this functional

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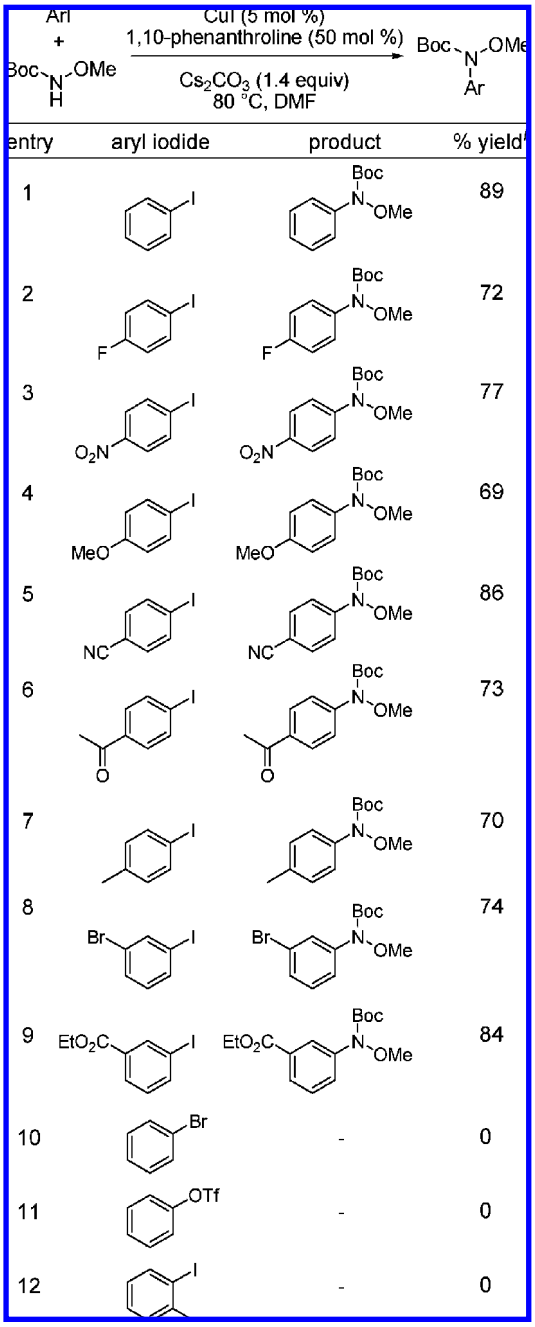
group in synthesis.[9−11] *N*-Aryl hydroxylamines are valuable in the preparation of nitrones,[12] aziridines,[13] electrophilic amination reagents,[14] and [3,3]-sigmatropic rearrangement processes,[15] as well as in the synthesis of indoles,[16] isoxazolidines,[17] oxadiazolidinones,[18] β-amino acids,[19] and β-amino alcohols,[20] each of which have found use in the preparation of pharmaceutical agents. As part of our ongoing research program to develop novel hydroxylamine-based reagents[21] we were interested in differentially protected *N*-aryl hydroxylamines and sought to develop methods to obtain this class of compound. Within this letter we describe an efficient method for the copper-catalyzed coupling of *N*,*O*-difunctionalized hydroxylamines with aryl iodides and methods for deprotection of the products for further synthetic manipulation.

Initial investigations examined the coupling of *N*-Boc-*O*-methyl hydroxylamine with iodobenzene. After examining a series of copper sources, ligands, bases, solvents, and temperatures the most efficient protocol was exploited as shown in Table 1. The coupling reaction proceeds smoothly in the presence of 5 mol % copper(I) iodide and 1,10-phenanthroline (50 mol %) as the ligand, using cesium carbonate as the base in DMF at 80 °C. The reaction was effective for a wide variety of aryl iodides with good to excellent yields (69−89%) and an outstanding functional group tolerance in the substrate including aryl-nitro, -nitrile, -keto, -ester, and -bromide functionalities (entries 1−9). It is also worth noting that under the conditions used within this study aryl bromides, aryl triflates, and 2-iodotoluene were ineffective as substrates for the coupling procedure (entries 10−12).

After effective conditions for the coupling were developed we examined the scope and limitations of the hydroxylamine coupling partner with the aim of introducing *N*- and

Table 1. Scope of the Aryl Halide Coupling Partner[a]



entry	aryl iodide	product	% yield[b]
1			89
2			72
3			77
4			69
5			86
6			73
7			70
8			74
9			84
10		-	0
11		-	0
12		-	0

[a] All reactions performed in duplicate at 0.5 M concentration of hydroxylamine. [b] Isolated yield.

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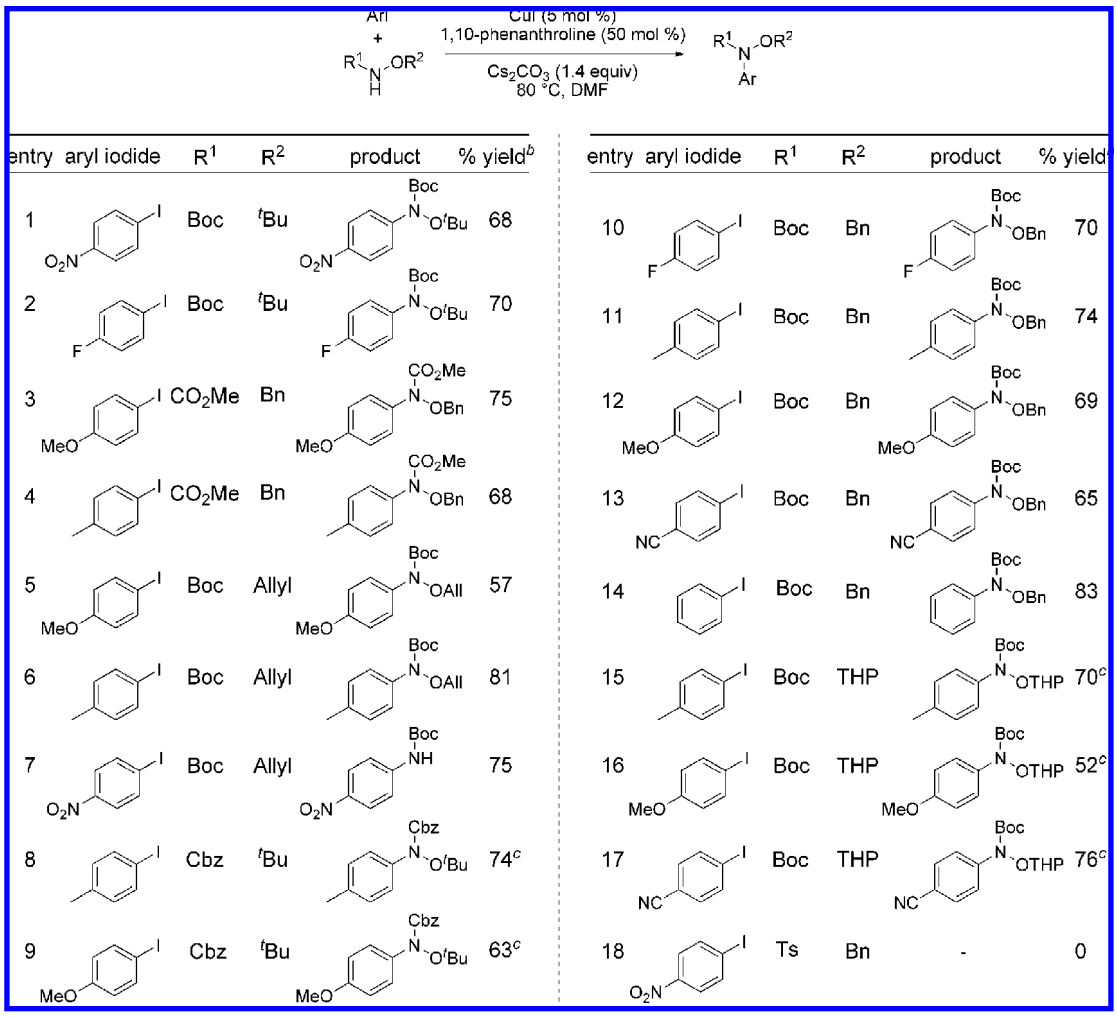
Table 2. Scope of the Hydroxylamine Coupling Partner[a]



entry	aryl iodide	R^1	R^2	product	% yield[b]
1		Boc	^{t}Bu		68
2		Boc	^{t}Bu		70
3		CO_2Me	Bn		75
4		CO_2Me	Bn		68
5		Boc	Allyl		57
6		Boc	Allyl		81
7		Boc	Allyl		75
8		Cbz	^{t}Bu		74[c]
9		Cbz	^{t}Bu		63[c]
10		Boc	Bn		70
11		Boc	Bn		74
12		Boc	Bn		69
13		Boc	Bn		65
14		Boc	Bn		83
15		Boc	THP		70[c]
16		Boc	THP		52[c]
17		Boc	THP		76[c]
18		Ts	Bn	-	0

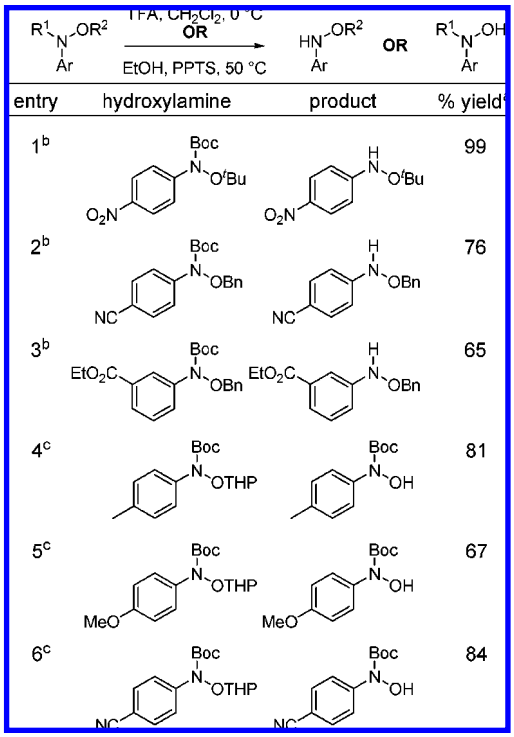
[a] All reactions performed in duplicate at 0.5 M concentration of hydroxylamine. [b] Isolated yield. [c] 10 mol % catalyst used.

O-substituents that could efficiently be removed to allow further functionalization of the hydroxylamine products (Table 2).

The conditions developed proved effective for a range of hydroxylamine coupling partners. With regard to the nitrogen substituent *tert*-butyl-, benzyl-, and methyl-carbamates all added efficiently in good to excellent yield (52−83%) with the oxygen substituents examined including *tert*-butyl, benzyl, tetrahydropyranyl, and allyl, suggesting the method should be effective for a variety of hydroxylamines. Limitations revealed with the process showed that care had to be taken with the coupling of some electron-deficient hydroxylamines and/or aryl iodides. Coupling of 4-nitro iodobenzene with *N*-Boc-*O*-allyl hydroxylamine resulted in the sole isolated product being that of concomitant N−O bond cleavage (75%, entry 7) and the reaction between 4-nitro iodobenzene and *N*-tosyl-*O*-benzyl hydroxylamine resulted in no *N*-arylation product being isolated from the reaction mixture (entry 18). With *N*-Cbz (entries 8 and 9) and *O*-THP hydroxylamines (entries 15−17) 10 mol % of catalyst was necessary to bring about efficient coupling. Despite these limitations, the broad range of couplings exemplified (Table 2) show this to be a robust and general coupling reaction of hydroxylamines and aryl iodides.

When selecting our hydroxylamine coupling partners, we elected to incorporate traditional *N*- and *O*-protecting groups to allow subsequent unmasking of these useful functionalities for further synthetic manipulation. A series of examples for deprotection of both the nitrogen and oxygen groups are outlined in Table 3. Removal of the Boc protecting group by treatment of the *N*-arylhydroxylamine with trifluoroacetic acid provided the free hydroxylamines in excellent yield (65−98%, entries 1−3). It was also possible to efficiently

Table 3. Deprotection of Coupled Products



[a] Isolated yield. [b] TFA, CH_2Cl_2, 0 °C, 1 h. [c] EtOH, PPTS, 50 °C, 2 h.

unmask the oxygen functionality while maintaining the integrity of the sensitive hydroxylamine bond. For example, the THP protecting group could easily be removed under mild hydrolytic conditions to give the expected products (67−84%, entries 4−6).

In summary, we have described a mild and efficient copper-catalyzed coupling of hydroxylamine derivatives with aryl iodides. The method is tolerant of a variety of functional groups in both the aryl and hydroxylamine coupling partners allowing for further synthetic manipulation. In addition, the products can be selectively *N*- or *O*-deprotected allowing full advantage of the versatility of this functional group to be realized. Exploitation of this work in the preparation of arrays of drug-like molecules is currently underway.

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Supporting Information Available: Analytical data, experimental procedures, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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