Palladium-Catalyzed Coupling of Hydroxylamines with Aryl Bromides, Chlorides, and Iodides
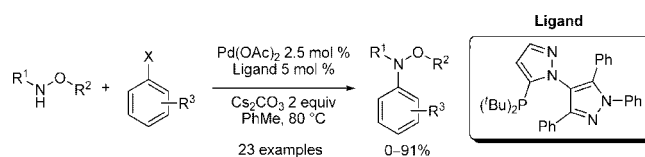
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ABSTRACT

The bis-pyrazole phosphine ligand BippyPhos is effective for the palladium-catalyzed cross-coupling of hydroxylamines with aryl bromides, chlorides, and iodides. Reactions proceed smoothly at 80 °C in toluene in the presence of Cs_2CO_3 to give synthetically versatile *N*-arylhydroxylamine products in good to excellent yield.

Over the past decade the palladium-catalyzed arylation of nitrogen-containing compounds (Buchwald−Hartwig amination) has emerged as a valuable tool in synthetic chemistry.[1] Extensive investigations have allowed for the coupling of a number of amine nucleophiles with aryl halides to provide a general route to a broad range of aniline derivatives and valuable heterocyclic ring systems.[2] Interestingly, despite the biological and synthetic significance of *N*-aryl hydroxylamines,[3] only three reports of palladium-catalyzed cross-

couplings of this functionality have been disclosed.[4,5] Each of these reports is limited to the coupling of *O*-homoallyl hydroxylamines in a useful tandem arylation/Heck sequence for the preparation of isoxazolidines. This lack of investigation is surprising as *N*-aryl hydroxylamines are valuable intermediates in the preparation of important nitrogen heterocycles such as indoles,[6] isoxazolidines,[7] oxadiazolidinones,[8] and aziridines,[9] among others.[10] *N*-Aryl hydroxylamines have also been studied as precursors for [3,3]-sigmatropic rearrangements to obtain 2-aminophenols through a formal C−H functionalization strategy.[11]

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As part of our ongoing research program to develop novel hydroxylamine based reagents,[12] we recently reported the copper-catalyzed N-arylation of hydroxylamines with aryl iodides.[13] Significant limitations to this process were that aryl bromides did not react, and *ortho*-substitution of the aryl iodide was not tolerated. Another drawback was the relatively high catalyst (up to 10%) and ligand (50 mol %) loadings and the use of 3 equiv of aryl iodide to bring about effective coupling. Within this Letter we describe an efficient and versatile method for the palladium-catalyzed coupling of hydroxylamines with aryl bromides, iodides, and chlorides that overcomes these problems, providing a considerably more practical and useful method for the arylation of this important functionality.

In an initial screen to establish the ability of palladium to promote the coupling of hydroxylamines we examined the reaction between N-Boc-O-TBDMS hydroxylamine (**1**) and bromobenzene (**2**) in array format under a standard set of conditions (2.5 mol % Pd; 5 mol % ligand; 2 equiv base; 60 °C; 0.25 M). Variables examined included palladium source ($Pd(OAc)_2$, $Pd(dba)_2$), base (Cs_2CO_3, NaO^tBu, K_3PO_4), solvent (dioxane, DMF, PhMe, DME), and a broad range of ligands (PCy_3, PPh_3, dppe, dppb, BINAP, dppf, Q-Phos,[14] DavePhos,[15] JohnPhos,[16] TrippyPhos,[17] BippyPhos[17]). Additionally, we also examined the palladium precatalyst PEPPSI within the transformation.[18] Remarkably, from this extensive reaction screen, only the Singer ligand BippyPhos (Figure 1) provided any of the desired coupling product **3**.
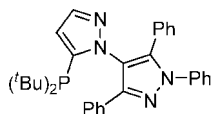

Figure 1. Singer ligand BippyPhos.

BippyPhos was developed as a nonproprietary ligand within Pfizer for the coupling of primary amines with aryl

halides overcoming problematic β-hydride elimination. It has subsequently been shown to be a general ligand for palladium-catalyzed amination reactions. Additionally, it is also effective for aryl ether formation and Suzuki−Miyaura reactions.[19] This current work highlights some of the unique potential of this readily accessible ligand in palladium-catalyzed processes.

A selection of the results using the BippyPhos ligand is shown in Figure 2. Although not all reactions were success-
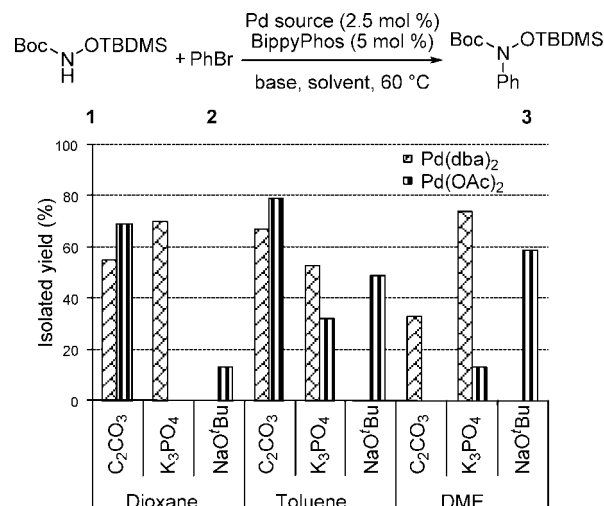
Figure 2. Screening results varying solvents and bases. Reaction conditions: Pd source (2.5 mol %); BippyPhos (5 mol %); **2** (1 equiv); base (2 equiv); 60 °C; 20 h; 0.25 M concentration hydroxylamine, PhBr (1 equiv).

ful, it is clear this ligand promotes the coupling reaction with a range of solvents, bases, and sources of palladium. The precise reason for all other ligands examined failing within the reaction is unclear at present, although the observation may explain that despite extensive reports on the Buchwald−Hartwig amination, examples of hydroxylamine couplings have been limited to those of homoallyl hydroxylamines.[4,5] With the solvent/base combination of cesium carbonate/toluene emerging from this initial screen as the most effective combination, we further optimized the process with regards temperature (80 °C), equivalents of aryl bromide (1.2 equiv), and concentration (0.5 M with respect to hydroxylamine) before examining the scope of the coupling procedure (Table 1).

Pleasingly, the reaction conditions developed had a broad substrate scope in both aryl halide and hydroxylamine coupling partners. Standard oxygen protecting groups on the hydroxylamine were well tolerated with *tert*-butyl and methyl carbamates (entries 1−6; 78−91%); however, amides were ineffective coupling partners (entry 7). Along with aryl bromides (entries 1−6), aryl iodides (entry 8; 90%) and aryl

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Table 1. Scope of Hydroxylamine Coupling[a]

$$R^1\text{-N(H)-}OR^2 \; + \; ArX \xrightarrow[\substack{Cs_2CO_3 \text{ (2 equiv)} \\ 80\,^{\circ}C, \; PhMe}]{\substack{Pd(OAc)_2 \text{ (2.5 mol \%)} \\ BippyPhos \text{ (5 mol \%)}}} R^1\text{-N(}OR^2\text{)-}Ar$$

(ArX 1.2 equiv)

entry	aryl halide	R^1	R^2	product	% yield[b]	entry	aryl halide	R^1	R^2	product	% yield[b]
1	PhBr	Boc	TBDMS	Boc-N(OTBDMS)-Ph	91	12	4-MeO-C₆H₄Br	Boc	TBDMS	Boc-N(OR²)-Ar(4-MeO)	84
2	PhBr	Boc	Bn	Boc-N(OBn)-Ph	80	13		Boc	THP		87
3	PhBr	Boc	Me	Boc-N(OMe)-Ph	80	14	4-O₂N-C₆H₄Br	Boc	THP	Boc-N(OR²)-Ar(4-NO₂)	88
4	PhBr	Boc	ᵗBu	Boc-N(OᵗBu)-Ph	85	15		Boc	TBDMS		74
5	PhBr	Boc	THP	Boc-N(OTHP)-Ph	82	16	4-Me-C₆H₄Br	Boc	THP	Boc-N(OTHP)-Ar(4-Me)	86
6	PhBr	CO₂Me	THP	CO₂Me-N(OTHP)-Ph	78	17	2-Me-C₆H₄Br	Boc	THP	Boc-N(OTHP)-Ar(2-Me)	55[c]
7	PhBr	PhCO	THP	COPh-N(OTHP)-Ph	0	18	4-THPO-C₆H₄Br	Boc	TBDMS	Boc-N(OTBDMS)-Ar(4-THPO)	85
8	PhI	Boc	TBDMS	Boc-N(OTBDMS)-Ph	90	19	4-acetyl-C₆H₄I	Boc	TBDMS	Boc-N(OTBDMS)-Ar(4-COMe)	74
9	PhCl	Boc	TBDMS	Boc-N(OTBDMS)-Ph	65	20	3-EtO₂C-C₆H₄I	Boc	TBDMS	Boc-N(OTBDMS)-Ar(3-CO₂Et)	68
10	PhOTf	Boc	TBDMS	Boc-N(OTBDMS)-Ph	<5	21	3-Br-C₆H₄I	Boc	TBDMS	Boc-N(OTBDMS)/Boc-N(OTBDMS) bis	65
11	PhBr	Boc	H	–	0	22	3-(dioxolanyl)-C₆H₄I	Boc	TBDMS	Boc-N(OTBDMS)-Ar(dioxolane)	91
						23	2-naphthyl-Br	Boc	THP	Boc-N(OTHP)-naphthyl	78

[a] Standard reaction conditions: Pd(OAc)₂ (2.5 mol %); BippyPhos (5 mol %); Cs₂CO₃ (2 equiv); 80 °C; 18 h; 0.5 M concentration of hydroxylamine; ArBr (1.2 equiv); toluene. [b] Isolated yield. [c] Reaction performed at 100 °C.

chlorides (entry 9; 65%) were also effective within the reaction. Aryl triflates did not couple efficiently under the standard conditions (entry 10; <5%). Protection of the hydroxylamine oxygen was found to be essential (entry 11), without which starting materials were recovered from the reaction. Functional group tolerance was also found to be outstanding with aryl-methoxy, -alkyl, -nitro, -keto, -ester, -halide, and -acetal being tolerated (entries 12–22; 55–91%).

Reaction of *ortho*-substituted partners proved difficult; however, simply heating the reaction mixture at 100 °C afforded the desired product in respectable yield (entry 17; 55%). With 3-bromoiodobenzene the reaction showed little discrimination between the iodide and bromide; running the reaction in the presence of 2 equiv of hydroxylamine provided the bis-functionalized product (entry 21; 65%). Overall, the broad range of couplings exemplified (Table 1)

show this to be a robust and general coupling reaction of hydroxylamines and aryl halides.

Finally, some potential for the hydroxylamine products was revealed following removal of the *O*-TBDMS group to give **4** (95%). Treatment of **4** with methanesulfonyl chloride (1 equiv) gave the protected 1,2-aminophenol **5** (91%) via *O*-sulfonation followed by [3,3]-sigmatropic rearrangement.[11a] In contrast, reaction of **4** with trifluoromethanesulfonic anhydride (1 equiv) gave the protected 1,4-aminophenol **6** (88%).[20]

In summary, we have described a mild and efficient palladium-catalyzed cross-coupling of protected hydroxylamines with a broad range of aryl bromides. Additionally, aryl iodides and aryl chlorides can also be used within the process. Key to the success of this protocol was the use of the Singer ligand BippyPhos; use of a range of alternative phosphine ligands failed to deliver the desired *N*-arylhydroxylamine products under the conditions examined. This procedure provides significant advantages over alternative methods for hydroxylamine couplings, including lower catalyst and ligand loadings, expansion of the scope of aryl coupling partner, improved functional group tolerance on the hydroxylamine, and compatibility with *ortho*-substitution on the aryl halide. The majority of the products described possess standard O- and N-protecting groups, allowing full advantage of the products to be realized.[21] Current work is focused on understanding the formation of **6** and introducing alternative nucleophiles into this intriguing rearrangement reaction.

Scheme 1. Deprotection and Conversion to 1,2- and 1,4-Amino Phenols
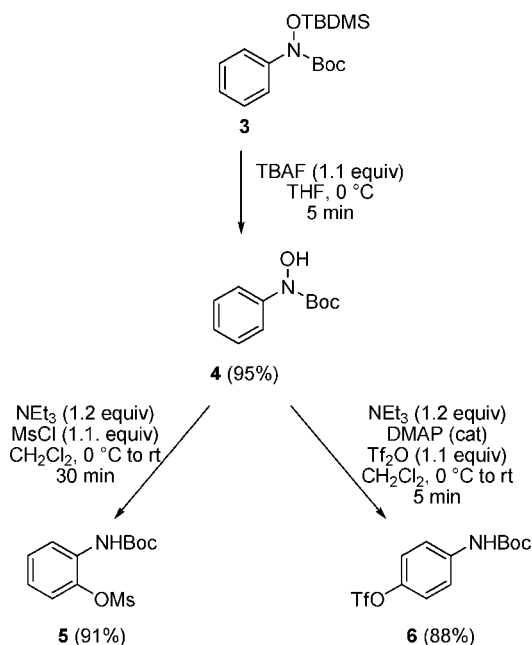
Supporting Information Available: Analytical data, experimental procedures, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The precise mechanism of this reaction is unknown at present; however, a related transformation has been described: Addition of *N*-phenyl hydroxylamine to trifluoromethanesulfonic acid (solvent) gives 4-*O*-trifluoromethanesulfonyl aniline (78%). See: Austin, R. P.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1411–1414.

(21) For example, for the selective removal of *N*-Boc or *O*-THP groups from protected *N*-aryl hydroxylamines, see ref 13.