# Copper(II)-Mediated *O*-Arylation of Protected Serines and Threonines

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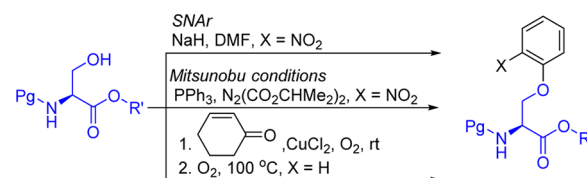
S *Supporting Information*

ABSTRACT: An effective protocol toward the *O*-arylation of β-hydroxy-α-amino acid substrates serine and threonine has been developed via Chan–Lam cross-coupling. This Cu(II)-catalyzed transformation involves benign open-flask conditions that are well-tolerated with a variety of protected (Boc-, Cbz-, Tr-, and Fmoc-) serine and threonine derivatives and various potassium organo-trifluoroborates and boronic acids.
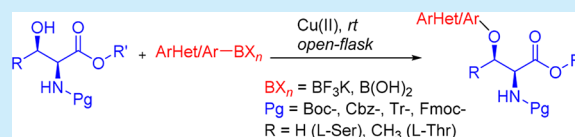
In nature, structural diversity in protein synthesis is achieved with a small number of naturally occurring amino acids. In the laboratory setting, the continuing development of novel reactions provides a much larger palette for exploring structural space, and indeed, on this basis, peptide synthesis has gone through major advances since the first report of peptide composition by Emil Fisher. In fact, unnatural peptides have now become a significant part of drug discovery efforts.[1] Among other chemical modification methods, cross-coupling reactions on peptides and proteins have received much attention, leading to selective formation of nonlabile linkages at residues functionally orthogonal to natural amino acids. Various unnatural amino acids synthesized via cross-coupling protocols can be genetically incorporated into peptides and proteins, leading to valuable protein modifications.[2] For example, the cross-coupling of 4-halophenylalanine, 4-boronophenylalanine, and L-tyrosine have been successfully accomplished.[3] In the same vein, β-hydroxy-α-amino acid derivatives have been used as constructs of drugs for the treatment of Alzheimer's disease (Figure 1, **I**) or inhibition of

Figure 1. Serine-containing biologically active compounds.

β-amyloid peptide release.[4] Benzoxazepinone **II** (Figure 1) was recently discovered as a potential target for cancer therapy.[5] It is noteworthy that compounds **I** and **II** are arylated at the *O*-site of serine.

To date, there are few general methods described for the *O*-arylation of L-serine. This transformation has been achieved by nucleophilic aromatic substitution, but this protocol is limited by the use of strong bases (NaH and KHMDS) and the need for 1-fluoro-2-nitrobenzene substrates.[4,5] Alternatively, the Mitsunobu

reaction affords the arylated product but with lowered yields. This protocol also requires triphenylphosphine as a reagent,[4b] resulting in tedious workup procedures. A new approach to the *O*-arylation of serine involves the copper-mediated reaction of nonaromatic precursors, α,β-unsaturated ketones, under aerobic conditions (Scheme 1), affording aromatized *O*-arylated

Scheme 1. Methods for Preparation of *O*-Arylated L-Serine

products. However, this protocol is substrate specific and requires higher temperatures, affording the *O*-arylated L-Ser in only 33% yield.[6] Thus, development of an efficient, mild and general method to arylate the hydroxyl position of L-serine to access structurally complex aryl alkyl ethers in natural products and pharmaceuticals remains a challenging goal.

This need has led to alternative methods for the synthesis of such structural motifs.[7] The direct formation of the C–O bond in alkyl aryl ethers by metal-catalyzed arylation of aliphatic alcohols with aryl halides is a formidable task compared to the classic Ullman-type synthesis of diaryl ethers because of the low reactivity of aliphatic alcohols.[7,8] Investigations by Buchwald and co-workers have shown that a reaction with Cu(I) salts in the presence of strongly basic alkoxides, performed under refluxing conditions, can efficiently promote the cross-coupling of aryl halides with phenols and aliphatic alcohols,[9] an alternative to the analogous Pd-catalyzed reactions developed by Buchwald and Hartwig.[10] It is noteworthy that Buchwald's conditions have been used on hydroxyproline methyl esters but failed to afford the
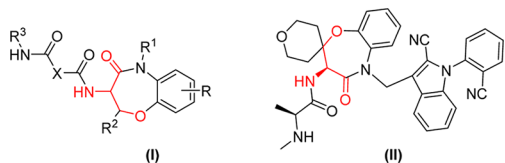
desired *O*-arylated products because of a lack of reactivity or elimination after the resulting arylation.[10g] Another protocol involves less common arylating agents such as organobismuths, but this approach requires in situ generation of the reagents by oxidation of the triarylbismuthine.[7,11]

In 1998, Chan,[12] Evans,[3a] and Lam[13] independently reported heteroatom arylation reactions that modernized alkyl-aryl ether synthesis. The development of this coupling reaction led to mild transformations that took place at room temperature under weakly basic conditions and could be carried out in an open reaction flask. For the C−O bond-forming reactions, this was limited primarily to phenols[3b,c,13,14] with the first examples utilizing catalytic amounts of $Cu(OAc)_2$ reported in 2001 by Lam.[8a,13] In addition to phenols, the development of copper-mediated C−O bond formation has flourished with the discovery that a broad range of oxygen nucleophiles, including carboxylic acids,[15] aliphatic alcohols,[8d] aryloximes,[16] silanols,[17] *N*-hydroxyphthalimides,[18] and water,[2a,19] have been coupled successfully from boron reagents using $Cu(OAc)_2$ as the catalyst of choice.

Herein, we report the first Chan−Lam cross-coupling of β-hydroxy-α-amino acid derivatives. The results reveal an effective and practical protocol for the formation of C−O alkyl aryl ethers from β-hydroxy-α-amino acid substrates serine and threonine, using benign conditions with both arylboronic acids and aryltrifluoroborates.

In an initial attempt at arylation, the reaction of Boc-L-Ser-OMe (**1a**) with both phenylboronic acid (**2a**) and potassium phenyltrifluoroborate (**2b**) in the presence of various copper catalysts, bases, and solvents in an open flask at room temperature was examined (Table 1). Comprehensive results and all screenings employed are shown in Table S1 of the Supporting Information). The use of CuI and $CuSO_4 \cdot 5H_2O$ with different catalyst loadings in the presence of Cs_2CO_3 and 1,10-phenanthroline using MeCN, CH_2Cl_2, or toluene as solvent was deemed ineffective (entries 1−6, Table 1). Anhydrous $Cu(OAc)_2$ (10 mol %) in the presence of DMAP (20 mol %) afforded the desired product in 75% yield when **2a** was utilized (entry 7, Table 1), but not in the case of **2b** (entry 7, Table 1). The use of $Cu(OAc)_2$ in pyridine and DMF as solvent was ineffective with both types of boron species (entry 9, Table 1). Fortunately, the reaction with $Cu(OAc)_2 \cdot H_2O$ in the presence of DMAP afforded the desired product with both **2a** and **2b** (entry 10, Table 1). We set out to examine the reaction conditions further in the presence of $Cu(OAc)_2 \cdot H_2O$. The use of excess **2b** (2 equiv, entry 11, Table 1) was deemed ineffective, while the most effective catalyst loading proved to be 10 mol % of $Cu(OAc)_2 \cdot H_2O$ (entries 10 and 12−13, Table 1). DMAP was found to be superior to tetramethylguanidine, DBU, and DIPEA, and its absence gave zero yield (entries 10, 14−16, 23, Table 1). The addition of water (10 mol %) has no apparent effect on the boronic acid reaction, but is believed to assist the trifluoroborate reaction by facilitating the hydrolysis of $PhBF_3K$. The use of $ClCH_2CH_2Cl$ at higher temperatures (60 °C) gave homocoupling and ether formation of **2a** or **2b** as major side reactions, and thus CH_2Cl_2 was the solvent of choice for such transformations (entries 17−22, Table 1).

Under the conditions developed, the scope and limitations of this coupling were evaluated (Schemes 2 and 3). Various aryl and heteroaryltrifluoroborates and boronic acids as well as a series of serine derivatives with different protecting groups and ester derivatives of L-Ser (Scheme 2) were employed. Several protecting groups, Boc- (**3a−e**), Cbz- (**3f−3p, 3s**), Tr-(**3q**), and the base-sensitive Fmoc- (**3r**) were well-tolerated. In general,

Table 1. Optimization of Reaction Conditions with Phenylboronic Acid and Potassium Phenyltrifluoroborate

entry	catalyst (10 mol %)	base/ligand (equiv)	yields of 3a (%) 2a, B(OH)$_2$	yields of 3a (%) 2b, BF$_3$K
1[a]	CuI	Cs$_2$CO$_3$ (3.0), 1,10-phen (0.2)	n.r.	n.r.
2[b,20]	CuI	Cs$_2$CO$_3$ (3.0), 1,10-phen (0.1)	n.r.	n.r.
3[b]	CuI	1,10-phen (0.2)	n.r.	n.r.
4[a]	CuSO$_4$·5H$_2$O	Cs$_2$CO$_3$ (3.0)	n.r.	n.r.
5[c]	CuSO$_4$·5H$_2$O	Cs$_2$CO$_3$ (3.0)	n.r.	n.r.
6[a]	CuSO$_4$·5H$_2$O		n.r.	n.r.
7	Cu(OAc)$_2$	DMAP (0.2)	75%	n.r.
8	Cu(OAc)$_2$	DMAP (1.0)	traces	n.r.
9[d,21]	Cu(OAc)$_2$	py (3.0)	n.r.	n.r.
10	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)	85%	80%
11[e,8d]	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)		traces[e]
12[f]	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)	65%	
13[g]	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)	81%	
14	Cu(OAc)$_2$·H$_2$O	tetramethylguanidine (0.2)	hc	hc
15	Cu(OAc)$_2$·H$_2$O	DBU (0.2)	hc	hc
16	Cu(OAc)$_2$·H$_2$O	DIPEA (0.2)	79%	70%
17[f,h]	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)	hc	hc
18[h]	Cu(OAc)$_2$·H$_2$O		n.r.	n.r.
19[a]	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)	n.r.	n.r.
20[i]	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)	60%	55%
21[j]	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)	84%	81%
22[k]	Cu(OAc)$_2$·H$_2$O	DMAP (0.2)	85%	87%
23	Cu(OAc)$_2$·H$_2$O		n.r.	n.r.

[a]CH_3CN. [b]Toluene. [c]$CuSO_4 \cdot 5H_2O$ (20 mol %). [d]$Cu(OAc)_2$ (150 mol %), DMF, under reflux.[8d] [e]$PhBF_3K$ (2 equiv). [f]$Cu(OAc)_2 \cdot H_2O$ (5 mol %). [g]$Cu(OAc)_2 \cdot H_2O$ (20 mol %). [h]$ClCH_2CH_2Cl$, 60 °C. [i]Dioxane. [j]O_2 balloon.[22] [k]O_2 balloon, H_2O (0.01 equiv). hc = homocoupling.

the reaction was unaffected by steric factors but was more sensitive to the electronic nature of the boron substrate as demonstrated by the yields.

Strongly electron-donating substituents with *p*-methyl (**3c**), *p*-ethyl (**3h**), *p*-isopropyl (**3i**), *p*-*tert*-butyl (**3j**), and *p*-N,N-dimethylamino (**3k**) afforded *O*-arylated L-serines in high yields. Electron-withdrawing substituents were also tolerated under the reaction conditions but gave lower yields, as in 3,5-trifluoromethyl (**3e**), *p*-trifluoromethyl (**3m**), and the *m*-nitrile (**3l**) substituted products. Both methyl and benzyl esters were examined, revealing that benzyl esters afford better yields (**3f** vs

Scheme 2. Substrate Scope of *O*-Arylation of L-Serine Derivatives
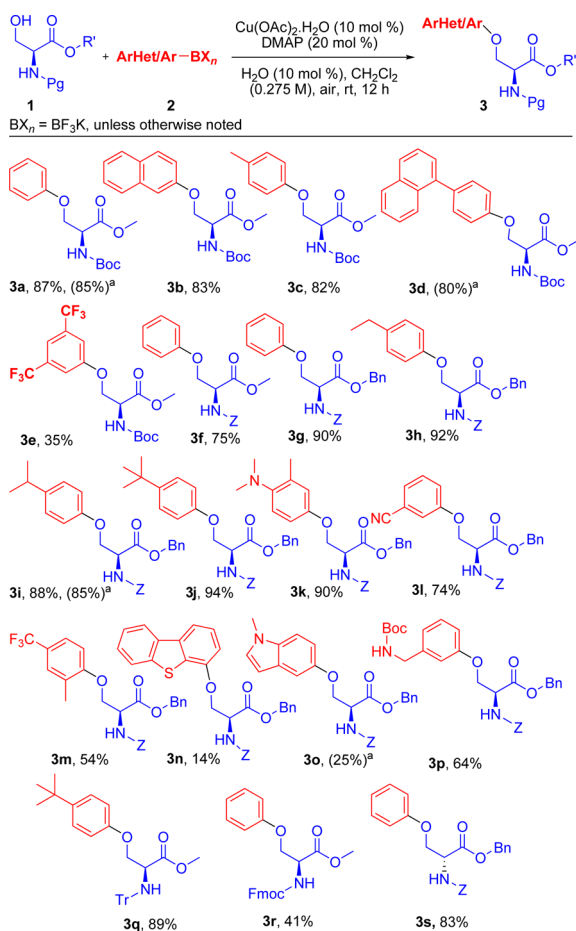
^{a}Ar/HetAr-BX$_n$ = B(OH)$_2$ was utilized, and no water was added to the reaction.

**Scheme 3. Substrate Scope of *O*-Arylation of L-Threonine Derivatives**
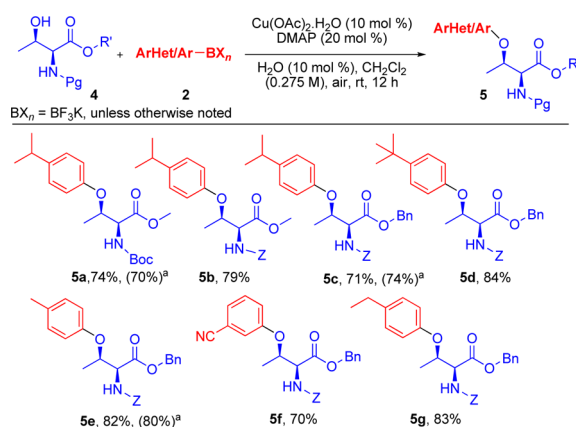
^{a}Ar/HetAr-BX$_n$ = B(OH)$_2$ was utilized, and no water was added to the reaction.

3g). Using bulky protecting groups, such as the trityl group in **3q**, as well as *o*-methyl (**3m**) and *m*-methyl (**3k**) substituents seemed to have no effect on the yield of the reaction. Although resulting in very low yields, we were pleased to observe that the reaction works with some heterocycles, including *N*-methylindole (**3o**

and dibenzothiophene (**3n**). However, the use of thiophenes and furans was detrimental, and no cross-coupling was observed when using organoboron reagents incorporating these ring systems. Instead, such substrates afforded unreacted starting materials and homocoupling as major side-products, especially at higher reaction temperatures.

We next turned our attention to applying this method to L-threonine (Scheme 3). With these substrates as well, the reaction conditions developed proved highly suitable and, most importantly, afforded single diastereomers with no epimerization observed. Both Boc- (**5a**) and Cbz- (**5b**–**5g**) protecting groups were employed and also proved to be well-tolerated.

Surprisingly, the reaction of Cbz-L-Ser-L-Thr-OMe **6** with 2 equiv of the phenyltrifluoroborate gave a single mono-*O*-arylated product **7** in 22% yield (eq 1). The mass spectral fragmentation
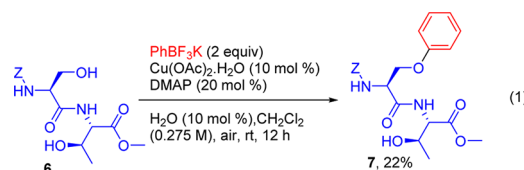

pattern of the product indicated that arylation took place selectively at the L-serine site (see Supporting Information). The use of dichloroethane at 60 °C led to more homocoupling and ether formation of the corresponding phenyltrifluoroborate, with no significant change in product formation.

In addition, we examined the reaction conditions using the phenolic OH of L-tyrosine as the nucleophile, and indeed, the reaction of Boc-L-Tyr-OMe **8** afforded the desired product **9** in 42% yield (eq 2).
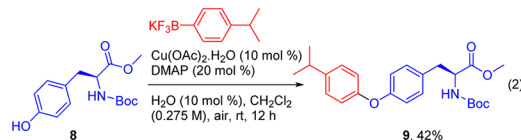
We also studied the side-products of this transformation. Interestingly, the reaction affords ethers of the corresponding boron reagents (Scheme 4), particularly with organoborons

Scheme 4. Ether Formation from the Corresponding Boron Reagents
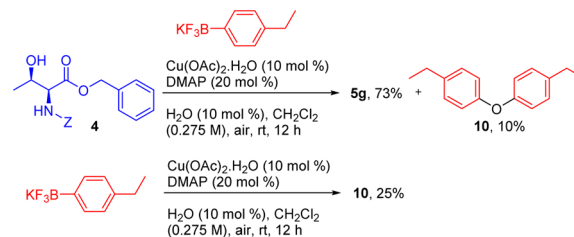
possessing electron-donating groups. The side-product ether **10** was obtained when the reaction was run under the same conditions but in the absence of the amino acid. We believe that this is the result of copper(II)-promoted oxidation of ArBF$_3$K[23] with subsequent participation of the resulting phenol in the cross-coupling.

Finally, the reaction performed under argon, in the absence of air/oxygen, with (4-isopropylphenyl)boronic acid did not progress and afforded no product after 48 h.

In conclusion, this is the first report for the Chan—Lam cross-coupling of serine and threonine derivatives, allowing access to novel unnatural β-aryloxy-α-amino acid derivatives. This new Cu(II)-catalyzed transformation involves mild conditions (rt, open flask) and is well-tolerated with a variety of protected (Boc-, Cbz-, Tr-, and Fmoc-) serine and threonine derivatives and various potassium organotrifluoroborates and boronic acids.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and product characterizations, ^{1}H and ^{13}C NMR spectra, mass spectral fragmentation for **7**, and Table S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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