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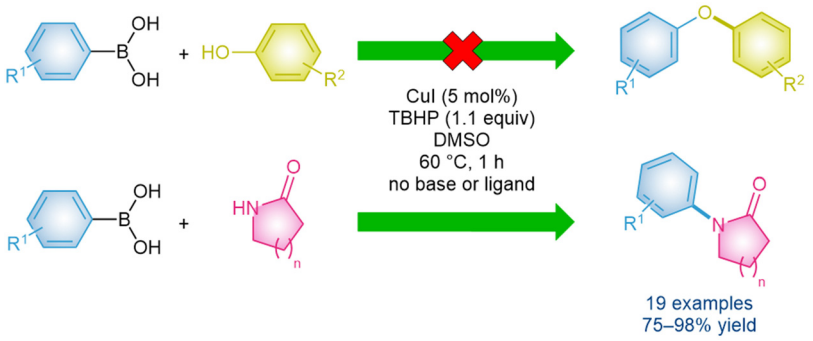
Selective Copper-Catalyzed N-Arylation of Lactams with Arylboronic Acids under Base- and Ligand-Free Conditions

Thulasiram Bathini
Vikas Singh Rawat
Bojja Sreedhar*

Inorganic & Physical Chemistry Division, Indian Institute of Chemical Technology (Council of Scientific & Industrial Research), Hyderabad – 500007, India
sreedharb@iict.res.in



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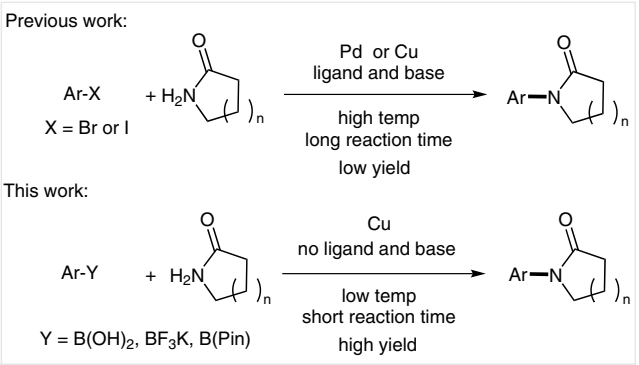
Abstract An oxidative copper-catalyzed cross-coupling of arylboronic acids with various ring-size lactams has been developed. The N-arylated lactams were obtained in moderate to excellent yields without any additional bases, ligands, or additives. This reaction shows complete selectivity for N-arylation of lactams in the presence of a hydroxyl group.

Key words amides, catalysis, copper, cross-coupling, oxidation

N-Arylated lactams are prevalent in various structurally diverse natural and pharmaceutical products.[1] For instance, the substituted *N*-aryl lactam unit is present in compounds that are potential candidates as anticancer,[2] antimicrobial,[3] antidiabetic,[4] CNS[5] and anticonvulsant[6] drugs. Moreover, substituted *N*-aryl lactams have also been used as key intermediates in the synthesis of various structurally complex heterocycles,[7] alkaloids,[8] and agrochemicals.[9] Given the wide range of applications, the synthesis of substituted N-arylated lactams has gained considerable attention in recent years.

The traditional approach used to access substituted *N*-aryl lactams involves transition-metal-catalyzed (Pd or Cu) cross-coupling reaction between substituted aryl halides with lactams, which facilitates variation of the aromatic component.[10–12] However, due to the relatively low nucleophilicity of lactams compared with amines, these coupling reactions often suffer from sluggish rates of reaction and low yields. Hence, many of these methods employ harsh reaction conditions such as high reaction temperatures or microwave heating. Recently, to improve the reaction conditions, several kinds of ligands such as diamines,[13] diimines,[14] amino acids,[15] β-keto esters,[16] and diols[17] have been used to promote this cross-coupling reaction. However, in spite of the vast improvement in reaction performance, this cross-coupling reaction still suffers from certain drawbacks such as the requirement for large amounts of catalyst, base, or ligand, or tedious workup procedures (Scheme 1).[10–17] Moreover, these methods are almost completely unselective with regard to other heteroatom nucleophiles such as alcohols, amines, or thiols, which raises an additional problem of chemoselectivity in this conversion.



Scheme 1

Despite these synthetic limitations, the cross-coupling of aryl halides with lactams remains the most viable method for accessing N-arylated lactams, and, consequently, chemoselectivity has become the main area of concern associated with such C(aryl)–N coupling reactions. In 2013, in an attempt to address this issue, Ranu et al. developed a Cu/Al_2O_3 catalyzed cross-coupling reaction of arylboronic acids with lactams by using K_3PO_4 as base at 110 °C. They succeeded in the N-arylation of lactams and amines by using different solvent systems (DMF and H_2O, respectively).[18] In a similar way, we have undertaken the challenge to perform N-arylation of lactams in the presence of a hydroxyl group, as an approach to a potentially key pharmacophore.[19]

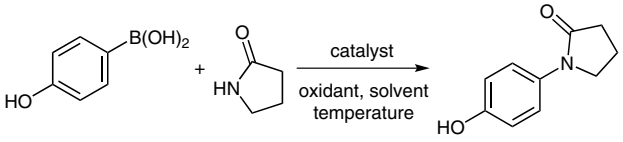
At the beginning of this work we opted for aryl boronic acid derivatives as an appropriate aryl source for this reaction. The logic behind this selection was to keep the reaction conditions mild, because it is well known that in C–N cross-coupling reactions the use of boronic acid derivatives instead of aryl halides leads to completion of the reaction at much lower temperatures.[20] For selective N-arylation optimization studies, we chose 4-hydroxyphenylboronic acid (**1a**) and pyrrolidin-2-one (**2a**) as our model substrates and, after some experimentation, the reaction afforded 1-(4-hydroxyphenyl)pyrrolidin-2-one (**3a**) as the sole product in 40% yield using 10 mol% $Cu(OAc)_2$ as catalyst in dimethyl sulfoxide (DMSO) at 80 °C in an open reaction vessel after 1 hour; no O-arylation product was detected. With this result in hand, we further examined the influence of parameters such as copper source, solvent, temperature, and amount of catalyst on this reaction. The results obtained from these studies are presented in Table 1. Initially we performed several comparative catalytic activity experiments by using various copper sources and found that, with the exception of $Cu(OAc)_2$, no other copper salts afforded **3a** in the presence of air. Similarly, reaction with $Cu(OAc)_2$ on rigorous exclusion of air and water gave only a 5% yield of **3a** (entry 2); performing reaction under an O_2 atmosphere resulted in a 50% yield of **3a** (entry 3).

Based on the above observations, it can be concluded that O_2 is required to obtain the desired product in this reaction. This is supported by the fact that, on addition of 1.1 equivalents of 70% aq TBHP, the yield of **3a** improved significantly to 80% (Table 1, entry 4). Hence, further comparative studies for copper sources were conducted using TBHP only. It was found that both $Cu(OAc)_2$ and CuI catalyzed this reaction efficiently with an overall yield of **3a** of 80 and 84%, respectively (entries 4 and 9). However, on running the reaction at lower catalyst loading (ca. 5 mol%), there was a marginal decrease in the yield of **3a** by 10% only in the case of $Cu(OAc)_2$ (entry 10); thus, further optimization was continued with 5 mol% CuI (entry 11). Moreover, a control experiment showed that no product was formed when the reaction was carried out in the absence of a copper catalyst (entry 12).

We then focused on the choice of oxidant for this reaction. It was observed that, among the various oxidants used, peroxide-based oxidants such as TBHP and H_2O_2 afforded **3a** in 84 and 74% yield, respectively (Table 1, entries 11 and 13). Solvent screening further established that DMSO was the preferred solvent for this reaction (entry 11). The obtained yields of **3a** with other solvents was as follows: THF (32%), MeCN (19%), dioxane (12%), and DMF (10%) (entries 18–21). In contrast to these results, the reaction in water, PEG-400, or ethanol did not afford **3a** at all (entries 22–24).

We found that the optimum reaction temperature for this transformation was 60 °C; use of this temperature resulted in 84% yield of **3a** (Table 1, entry 27). Higher or lower temperatures had a notably negative impact on the yield of **3a** (entries 25, 26, and 28). It was also observed that an increase in reaction time had no positive influence on the

Table 1 Optimization of Reaction Parameters[a]



1a **2a** **3a**

Entry	Catalyst	Oxidant	Solvent	Temp (°C)	Yield (%)[b]
1	$Cu(OAc)_2$	air	DMSO	80	40[c]
2	$Cu(OAc)_2$	–	DMSO	80	5[c]
3	$Cu(OAc)_2$	O_2	DMSO	80	50[c]
4	$Cu(OAc)_2$	TBHP	DMSO	80	80[c]
5	$Cu(OTf)_2$	TBHP	DMSO	80	70[c]
6	$CuCl_2$	TBHP	DMSO	80	78[c]
7	Cu	TBHP	DMSO	80	63[c]
8	CuBr	TBHP	DMSO	80	73[c]
9	CuI	TBHP	DMSO	80	84[c]
10	$Cu(OAc)_2$	TBHP	DMSO	80	70
11	CuI	TBHP	DMSO	80	84
12	–	TBHP	DMSO	80	0[d]
13	CuI	H_2O_2	DMSO	80	74
14	CuI	$PhI(OAc)_2$	DMSO	80	52
15	CuI	NaOCl	DMSO	80	20
16	CuI	$(NH_4)_2S_2O_8$	DMSO	80	–
17	CuI	O_2	DMSO	80	49
18	CuI	TBHP	THF	80	32
19	CuI	TBHP	MeCN	80	19
20	CuI	TBHP	dioxane	80	12
21	CuI	TBHP	DMF	80	10
22	CuI	TBHP	H_2O	80	0
23	CuI	TBHP	PEG-400	80	0
24	CuI	TBHP	EtOH	80	0
25	CuI	TBHP	DMSO	25	52
26	CuI	TBHP	DMSO	40	63
27	CuI	TBHP	DMSO	60	84
28	CuI	TBHP	DMSO	100	62
29	CuI	TBHP	DMSO	60	81[e]
30	CuI	TBHP	DMSO	60	78[f]

[a] Reaction conditions: pyrrolidin-2-one (3.0 mmol), (4-hydroxyphenyl)boronic acid (1.0 mmol), catalyst (5 mol%), oxidant (1.1 mmol), solvent (1.0 mL), 1 h.
[b] Isolated yield.
[c] 10 mol% catalyst.
[d] Reaction without catalyst.
[e] Reaction with 4-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)phenol.
[f] Reaction with 4- hydroxyphenyltrifluoroborate.

reaction yield. Additionally, the use of boronic acid derivatives such as 4-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)phenol or potassium 4-hydroxyphenyltrifluoroborate afforded **3a** in 81 and 78% yields, respectively (entries 29 and 30). Notably, unlike other known methods, this protocol does not require an additional base or ligand to proceed. Critically, no O-arylation was observed during optimization. Moreover, unlike the protocol developed by Ranu et al., the reaction rates here are generally fast and proceed to completion in about one hour and at much lower temperature.[18] Interestingly, quinone formation through oxidation of (4-hydroxyphenyl)boronic acid was not observed.[21] Furthermore, a competition experiment with a 1:1 mixture of pyrrolidin-2-one and phenol with phenylboronic acid resulted in the formation of 1-phenylpyrrolidin-2-one (**3b**) as the sole product (82% yield) without any diphenyl ether being observed. This N/O-selectivity for arylation found here is far better than that obtained by Buchwald et al., in the CuI-catalyzed arylation of β-amino alcohol, using NaOH as a base and DMSO/H_2O as the solvent system.[22] In their system, N/O-selectivity was achieved with a ratio greater than 20:1 when a β-diketone was used as the ligand. This observed selectivity is particularly important for substrates having multiple N- and O-heteroatom sites that are capable of undergoing N-arylation reaction, hence giving potential for short, rapid, and protecting-group-free synthesis of molecules of great complexity.

After establishing the optimized reaction conditions [Table 1, entry 27; amide (3.0 equiv), arylboronic acid (1.0 equiv), CuI (5 mol%), aq TBHP (70%, 1.1 equiv), DMSO, 60 °C] we further explored the generality and functional group compatibility of this reaction on various structurally diverse boronic acids; the results are presented in Table 2.

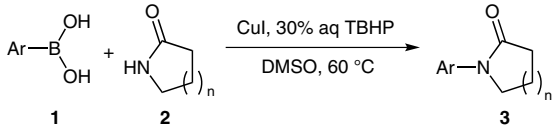
The reaction proceeded smoothly with various aryl boronic acids **1** and ring size lactams **2** to afford N-arylated lactams **3b**–**s** in good to excellent yields. The nature of the aromatic substituents on the arylboronic acids has a remarkable influence on the outcome of the reaction, and it was observed that the reaction favors arylboronic acids having electron-withdrawing substituents.

For instance, the use of boronic acid **1f**, having a strong electron-donating substituent, and **1o**, with a strong electron-withdrawing substituent, afforded the desired N-arylated lactams **3h** and **3q** in yields of 77 and 95%, respectively (Table 2, entries 7 and 16). In this protocol, halide-substituted boronic acids **1h**–**m** were tolerated well, with no competitive cross-coupling reaction (entries 9–14); hence, providing the potential for further functionalization of the aryl ring. Similarly, when 1,4-phenylenediboronic acid (**1n**) was reacted with **2a**, only mono-N-arylated product **3p** was obtained (86%; entry 15).

To our satisfaction, no competing side reaction leading to the formation of *p*-cresol from *p*-tolylboronic acid **1d** was observed under these oxidizing conditions, and the reaction led to the formation of 1-(*p*-tolyl)pyrrolidin-2-one (**3f**) in 82% yield (Table 2, entry 5).[23] Notably, this catalytic system shows excellent catalytic activity with heterocyclic boronic acids such as 3-pyridinylboronic acid (**1q**), and the reaction gave the corresponding 1-(pyridin-3-yl)pyrrolidin-2-one (**3s**) in 78% yield (entry 18). Further investigation is required to reveal the precise nature of this catalytic system and to explain the observed chemoselectivity; this will form part of our future communications.

In conclusion, we have developed a facile and efficient CuI-catalyzed method for the N-arylation of lactams with arylboronic acids in DMSO at 60 °C. Reaction variables such as copper salt, temperature, and solvent were systematically optimized. The N-arylation of various ring-size lactams gave the corresponding N-arylated products in moderate to excellent yields. Many limitations of pre-existing methods such as elevated reaction temperatures, long reaction times, high metal loadings, and narrow substrate scope have been overcome by using this protocol. This catalytic system can

Table 2 Synthesis of Substituted *N*-Aryl Lactams[a]



1 2 3

Entry	Ar	1	*n*	2	3	Yield (%)[b]
1	Ph	**1b**	1	**2a**	**3b**	84
2	Ph	**1b**	3	**2b**	**3c**	90
3	2-naphthyl	**1c**	1	**2a**	**3d**	82
4	2-naphthyl	**1c**	2	**2c**	**3e**	85
5	4-MeC_6H_4	**1d**	1	**2a**	**3f**	82
6	4-*t*-BuC_6H_4	**1e**	2	**2c**	**3g**	80
7	4-$MeOC_6H_4$	**1f**	1	**2a**	**3h**	77
8	3,4-$(MeO)_2C_6H_3$	**1g**	1	**2a**	**3i**	75
9	4-FC_6H_4	**1h**	1	**2a**	**3j**	97
10	4-F-3-MeC_6H_3	**1i**	1	**2a**	**3k**	98
11	4-ClC_6H_4	**1j**	1	**2a**	**3l**	95
12	3,5-$Cl_2C_6H_3$	**1k**	1	**2a**	**3m**	97
13	3-BrC_6H_4	**1l**	1	**2a**	**3n**	92
14	4-IC_6H_4	**1m**	1	**2a**	**3o**	90
15	4-$(HO)_2BC_6H_4$	**1n**	1	**2a**	**3p**	86
16	3-$O_2NC_6H_4$	**1o**	1	**2a**	**3q**	95
17	4-(MeOCO)C_6H_4	**1p**	1	**2a**	**3r**	83
18	3-Py	**1q**	1	**2a**	**3s**	78

[a] Reaction conditions: amide (3.0 mmol), arylboronic acid (1.0 mmol), CuI (5 mol%), aq TBHP (70%, 1.1 mmol), DMSO (1.0 mL), 60 °C, 1 h.
[b] Isolated yield.

be used to achieve selective N-arylation even in the presence of a hydroxyl group. Moreover, the catalytic system is base- and ligand-free.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380741.

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(24) **Typical Procedure:** Aryl boronic acid (1.0 mmol), CuI (5 mol%), amide (3.0 mmol), and DMSO (1.0 mL) were added to a reaction vial, and the mixture was stirred at room temperature for 10 min. A 70% aqueous solution of TBHP (1.1 mmol) was added to the reaction mixture dropwise over 5 min. The reaction vial was then immersed in a preheated oil bath and the progress of reaction was followed by TLC. Upon completion of reaction, the cooled mixture was partitioned between water and ethyl acetate. The aqueous layer was further extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate) to give the desired *N*-aryl lactam.

(25) **1-(4-Hydroxyphenyl)pyrrolidin-2-one (3a):** Yield: 149 mg (84%); dark-red solid; mp 165–167 °C (Lit.[1] 167 °C). IR (KBr): 3134, 2926, 1686, 1650, 1517, 1413, 1308, 1274, 1235, 1203, 1220, 833, 657, 507, 460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, 2 H, *J* = 9.0 Hz), 6.78 (d, 2 H, *J* = 8.8 Hz), 3.82 (t, *J* = 6.9, 7.1 Hz, 2 H), 2.61 (t, *J* = 7.9, 8.3 Hz, 2 H), 2.11–2.21 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 153.4, 131.7, 122.7, 115.7, 49.7, 32.3, 18.0. MS (ESI): *m*/*z* = 178 $[M + H]^+$. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{12}O_2N$: 178.0862; found: 178.0863.