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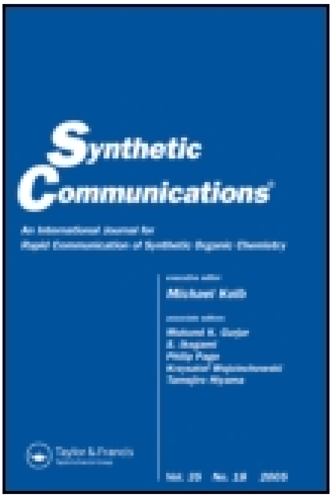

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Copper(I) 3-Methylsalicylate Mediates the Chan-Lam N-Arylation of Heterocycles

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COPPER(I) 3-METHYLSALICYLATE MEDIATES THE CHAN–LAM *N*-ARYLATION OF HETEROCYCLES

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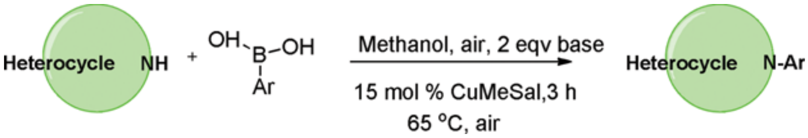
GRAPHICAL ABSTRACT



Abstract *Copper(I) 3-methylsalicylate (CuMeSal) mediates* N*-arylation reactions between aryl boronic acids and aromatic heterocycles (Chan–Lam coupling) under moderate reaction conditions (K_2CO_3, methanol, 65 °C, in air, 3–5 h). Both electron-rich and electron-deficient aryl boronic acids and a diverse set of* N*-heterocycles were allowed to react and gave* N*-arylation products in reasonable yields, which demonstrate the utility of this catalyst.*

Keywords C-N bond formation; Chan–Lam coupling; copper(I) 3-methylsalicylate; *N*-arylation

INTRODUCTION

The ability to directly form heterocyclic aryl C-N bonds is of importance to synthetic chemists engaged in medicinal and natural product chemistry research. In recent years significant attention has been focused on metal-mediated reactions, leading to the formation of C-N bonds. These studies have primarily concentrated on Ullmann (Cu-mediated)[1] and Buchwald–Hartwig (Pd-mediated)[2] coupling reactions. Considerable attention has been given to optimization of the copper-mediated processes because it is the more economical and less toxic of the two metals. The preponderance of these studies has focused on reactions between *N*-heterocycles and aryl halides with extensive efforts directed toward optimization of the copper source, ligand, base, and solvent.[3] As a consequence, a number of attractive alternatives to the original Ullman process for coupling with aryl halides are available.

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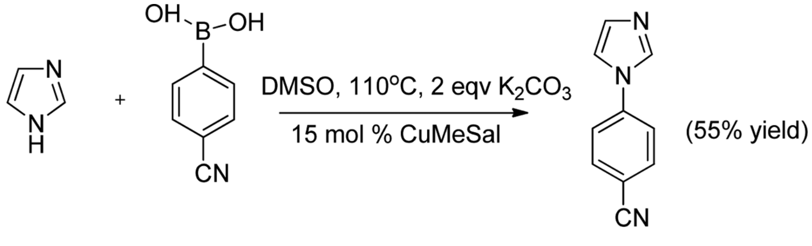
In 1998 researchers[4–6] reported a variation in the Ullmann process that replaced the aryl halides with aryl boronic acids, which significantly expands the scope of this reaction. The Chan–Lam process has been the subject of intensive investigations with similar goals of optimizing the reaction.[7] Many of these studies have focused on the pairing of effective copper ion sources with various ligands, whereas relatively limited attention has been given the use of defined copper complexes. The reaction of imidazole and aryl boronic acids mediated by a synthetic sulfonato-Cu-salen complex in water at 100 °C gave good to excellent yields of *N*-arylimidazoles[8] and a more recent report has shown that a related synthetic Cu–salen complex mediated the *N*-arylation of imidazole and benzimidazole with aryl boronic acids in good yields at room temperature in 2-propanol.[9] We recently reported that commercially available copper(I) 3-methylsalicylate (CuMeSal) mediated the reaction between aryl bromides and various *N*-heterocycles in excellent yields.[10] To our knowledge the use of CuMeSal for Chan–Lam coupling has not been reported for *N*-arylation. This report describes our efforts to evaluate CuMeSal as a possible Chan–Lam coupling mediator.

RESULTS AND DISCUSSION

Previously, we had determined that dimethylsulfoxide (DMSO) was the most effective solvent for the CuMeSal-mediated reaction between aryl bromides and *N*-heterocycles;[10] hence in our initial experiment using aryl boronic acids as the aryl donor we used DMSO as the solvent. When 4-cyanophenyl boronic acid and imidazole was allowed to react for 3 h in DMSO, in air, at 110 °C in the presence of 15 mol% CuMeSal and 2 eqv of K_2CO_3, we were pleased to see that a moderate isolated yield (55%) of 1-(4-cyanophenyl)-1-*H*-imidazole was obtained (Scheme 1). Seeking to improve the yield we explored the same reaction in a number of different solvents (Table 1). We found that alcohols were the most effective solvents with methanol (77% yield), giving a slightly greater yield than *i*-propanol (74% yield).

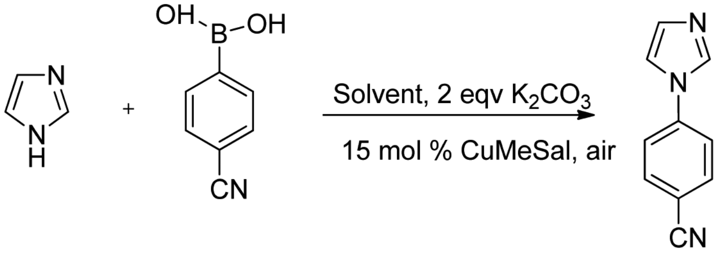
Next we examined the impact of catalyst load (ranging from 5 to 25 mol%) on the yield of the reaction between 4-cyanophenyl boronic acid and imidazole in methanol (Table 2). The two lowest loads of CuMeSal (5 and 10 mol%) gave lower isolated yields (53% and 61%, respectively) than the 15 mol% load (77% isolated yield). Raising the catalyst load to 20 or 25 mol% did not significantly change the yield (79%) obtained compared to that obtained with 15 mol%. Consequently, in subsequent experiments we used 15 mol% for all the coupling reactions.

In additional efforts to improve the yield we examined the use of several other bases as shown in Table 3. Cesium and potassium carbonate gave the greatest yields,



Scheme 1. Reaction of imidazole with 4-cyanophenylboronic acid.

Table 1. Effects of solvent, temperature, and reaction time

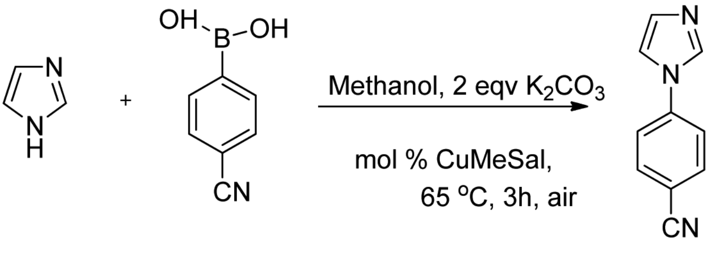


Solvent	Temp. (°C)	Time (h)	Isolated yield (%)
DMSO	110	3	55
NMP	110	3	43
DMF	110	3	51
DMA	110	12	Trace
Toluene	110	12	Trace
Dioxane	101	12	28
Isopropanol	82	3	74
Methanol	65	3	77
Ethanol	78	3	69

with the former giving slightly greater value. Because the two bases were essentially equally effective, we used potassium carbonate in the subsequent studies for economic reasons.

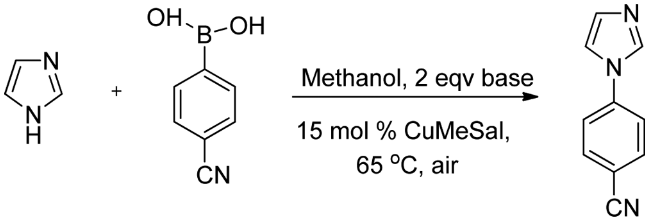
Table 4 contains the results of the effects of structures of both the aryl boronic acid and the *N*-heterocycle on the yield of the CuMeSal-mediated Chan–Lam process. The electronic effects of substituents on the aryl boronic acid when coupled with imidazole show a modest effect on the yield of the *N*-aryl imidazoles. The isolated yields range from a high of 82% for the electron-attracting *p*-nitro group

Table 2. Effects of mol% of catalyst



Amount (mol%) catalyst	Isolated yield (%)
5	53
10	61
15	77
20	79
25	79

Table 3. Effects of base

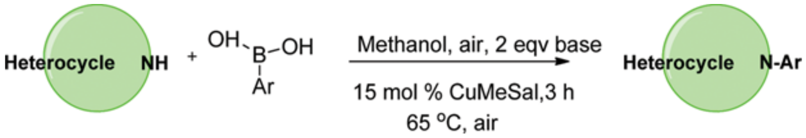


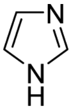
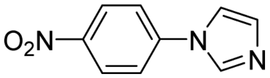
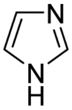
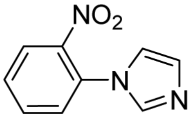
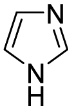
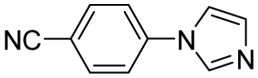
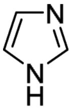
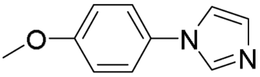
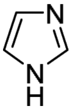
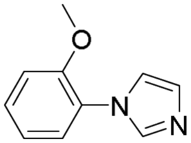
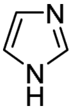
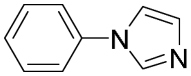
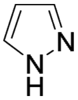
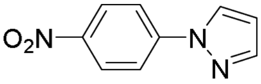
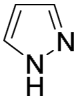
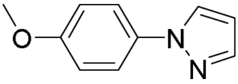
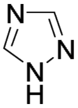
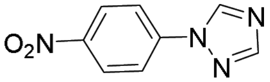
Base	Time (h)	Isolated yield (%)
Cs_2CO_3	3	80
K_2CO_3	3	77
K_3PO_4	12	15
Na_2CO_3	12	58
Et_3N	12	Trace

to a low of 69% for the electron-donating *p*-methoxy group. A similar trend was noted for the CuMeSal-mediated coupling of aryl bromides and imidazole,[10] and the original Lam conditions using $Cu(OAc)_2$ for coupling imidazole with aryl boronic acids showed a similar substituent effects trend.[6] However, other studies using various copper salt/ligand combinations for formation of *N*-arylimidazoles show no clear substituent effect trend.[11] On examination of the results for the imidazole coupling reaction with *o*-nitrophenyl boronic acid and *o*-methoxyphenyl boronic acid we note that steric effects play an important role on the yield under our conditions. In comparison to the results obtained with the *p*-isomers a greater than 2-fold reduction in yield was noted; the isolated yield for the *o*-nitro isomer is 35% and that for the *o*-methoxy one is 24%. The steric effect for the CuMeSal-mediated reaction of imidazole with related *o*-substituted aryl bromides was significantly less.[10] However, Chan–Lam couplings using $[Cu(OH)TMEDA]_2Cl_2$ showed a similar sensitivity to steric effects.[12] In contrast, a study using CuCl as the copper source showed essentially no sensitivity to steric interactions.[13] To gain a better understanding of both substituent electronic and steric effects on the course of Chan–Lam reactions, careful studies employing a range of substituted aryl boronic acids, hindered *N*-heterocycles, and different copper sources under standardized conditions are needed.

Catalyst systems have been reported which successfully use alkyl boronic acids in Chan–Lam coupling processes with *N*-heterocycles.[14] However, under the conditions presented here we failed to detect the formation of coupling between imidazole and methyl, cyclopropyl, or cyclopentyl boronic acids. Cross-coupling between boronic esters and N-heterocycles under various Chan–Lam conditions have been reported, although the yields are often poor.[15] However, under our conditions no evidence of coupling was found between imidazole and *p*-nitrophenylboronic acid pinacol ester. In the case of the CuMeSal-mediated reactions of aryl bromides with N-heterocycles we also found that nonaromatic heterocycles such as pyrrolidine were also coupled in good yields.[10] However, under our standard conditions here we did not detect the formation of a coupling product between pyrrolidine and *p*-nitrophenylboronic acid.

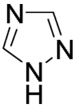
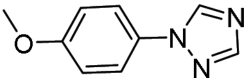
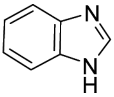
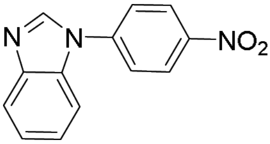
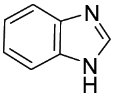
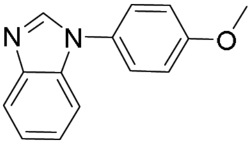
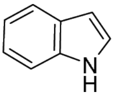
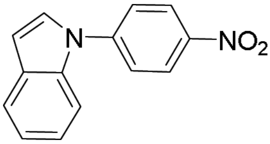
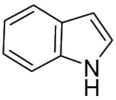
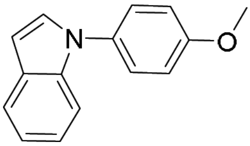
Table 4. Reactions of different *N*-containing heterocycles with different aryl boronic acids under the optimized reaction conditions



N-Heterocycle	Ar	Product	Isolated yield (%)
	*p*-Nitrophenyl		82
	*o*-Nitrophenyl		35
	*p*-Cyanophenyl		77
	*p*-Methoxyphenyl		69
	*o*-Methoxyphenyl		24
	Phenyl		71
	*p*-Nitrophenyl		78
	p-OMe		74
	*p*-Nitrophenyl		84

(*Continued*)

Table 4. Continued

N-Heterocycle	Ar	Product	Isolated yield (%)
	*p*-Methoxyphenyl		77
	*p*-Nitrophenyl		75^a
	*p*-Methoxyphenyl		65^a
	*p*-Nitrophenyl		72^a
	*p*-Methoxyphenyl		67^a

^{a}Reaction time = 5 h.

In contrast, Chan–Lam coupling of aliphatic amines with aryl boronic acids using copper acetate[16] or copper oxide[17] gave good to excellent yields.

In addition to coupling aryl boronic acids with imidazole we obtained the results of reaction conditions with the coupling of *p*-nitrophenyl and *p*-methoxyphenyl boronic acid with pyrazole, 1*H*-2,4-triazole, benzimidazole, and indole (Table 4). The results with pyrazole and 1*H*-2,4-triazole were similar to those noted with imidazole, and in all cases the coupling with *p*-nitrophenylboronic acid gave a somewhat greater yield than obtained with *p*-methoxyphenylboronic acid. A similar result was found for the coupling with benzimidazole and indole, although the reaction times needed to be increased from our standard 3 h time to 5 h to achieve the indicated yields. This difference may reflect a moderate steric effect from the *peri*-like 7-protons of the two fused ring heterocycles.

In conclusion we have shown, for the first time, that commercially available CuMeSal mediates Chan–Lam arylation of N-heterocycles in reasonable yields under moderate conditions. This methodology is not as robust as the similar one using aryl bromides[10] and it appears less efficient than the Chan–Lam protocols employing the synthetic Cu-salens.[8,9] Nevertheless, the methodology reported here provides a useful alternative for performing Ullmann-type *N*-arylations.

EXPERIMENTAL

All commercial reagents were used without purification. Melting points were determined on a Mel-Temp 3.0 melting-point apparatus and are uncorrected. Thin-layer chromatographic (TLC) analysis was carried out on silica gel 60 F254 precoated aluminum sheets using ultraviolet light for detection. ^{1}H NMR spectra were recorded on a 400-MHz spectrometer using the indicated solvents. High-resolution mass spectra (HRMS) were obtained from the Georgia State University Mass Spectrometry Laboratory, Atlanta, GA.

General Method of *N*-Arylation

A dry flask was charged with the nitrogen-containing heterocycles (1 mmol), aryl boronic acids (2.2 mmol), potassium carbonate (2 mmol), and CuMeSal (0.015 mmol) and then anhydrous methanol (10 ml) was added. The reaction mixture was stirred at 65 °C, open to air, for 3 h (5 h in case of indole and benzimidazole), cooled to room temperature, and filtered, and the precipitate was washed with methanol (2 ml). The filtrate was concentrated under vacuum, then stirred with ice water (30 ml), extracted with ethyl acetate (3 × 50 ml), and dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by chromatography or recrystallization as indicated with each compound in the Supplementary Material. Spectral data and references to previously reported data for each compound are also provided in the Supplementary Material.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

FUNDING

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