



**A quick Chan-Lam C-N and C-S cross coupling at room temperature in presence of square pyramidal [Cu(DMAP)4I]I as catalyst**

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| Journal:                      | <i>ChemComm</i>  |
| Manuscript ID                 | CC-COM-06-2015-004619.R2   |
| Article Type:                 | Communication  |
| Date Submitted by the Author: | 16-Oct-2015  |
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# A quick Chan-Lam C-N and C-S cross coupling at room temperature in presence of square pyramidal [Cu(DMAP)<sub>4</sub>]I as catalyst

Received 00th January 20xx,  
Accepted 00th January 20xx

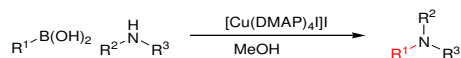
DOI: 10.1039/x0xx00000x

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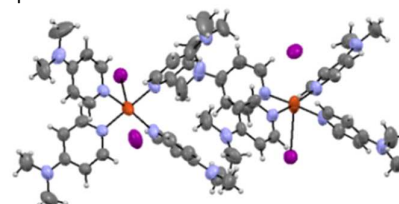
**Abstract** A rapid and efficient protocol for C-N and C-S cross coupling has been developed using a new square pyramidal copper complex [Cu(DMAP)<sub>4</sub>]I. The complex was successfully synthesized via a disproportionation reaction of CuI and DMAP in DMSO. Catalytic activity of the complex was found to be excellent for Chan-Lam coupling reaction between aryl boronic acid and amine, azide or thiol. Reaction could be carried out in presence of only 2 mol% of the copper catalyst in methanol at room temperature within a short time.

Formation of carbon-hetero atom bond is a very important transformation in organic synthesis. During past several decades, a variety of methods has been developed for C-N and C-S bond forming reactions using different catalyst derived from transition metals such as Pd, Fe, Ni, Cu etc.<sup>1</sup> In the year 1998, a mild protocol for Cu-mediated oxidative amination of aryl boronic acid was developed independently by Chan, Evans and Lam.<sup>2</sup> Thereafter, a number of modifications have been made to improve the yield and efficiency of Chan-Lam reaction using different copper salts in presence of various ligands, which include important examples such as Cu(OAc)<sub>2</sub>,<sup>3</sup> CuCl,<sup>4</sup> Cu(OTf)<sub>2</sub>,<sup>5</sup> CuF<sub>2</sub>,<sup>6</sup> Cu-β-Cyclodextrin complex<sup>7</sup> etc. Besides these examples on Chan-Lam coupling reaction, there are also other reports in the literature for C-N and C-S bond formation reactions in presence of various metals such as Cu,<sup>8</sup> Pd,<sup>9</sup> Ni,<sup>10</sup> Fe<sup>11</sup> etc. However, long reaction time and high reaction temperature are the most common issues that caused inconveniences in undertaking many of these methods for Chan-Lam coupling. Hence, modifications have been proposed to improve the process using microwave irradiation which could significantly cut-short the reaction time.<sup>12</sup> In this communication, we report very fast and efficient protocol for the Chan-Lam reaction using square pyramidal [Cu(DMAP)<sub>4</sub>]I complex as catalyst (Scheme 1).



**Scheme 1.** Chan Lam coupling of amines and boronic acid. The square pyramidal copper complex, [Cu(DMAP)<sub>4</sub>]I was

synthesized by disproportionation reaction of CuI in presence of DMAP. Initially, different solvents such as methanol, acetonitrile, 1:1 mixture of methanol and acetonitrile and DMSO were examined find a suitable condition for the formation of the copper complex. Synthesis was carried out by stirring a mixture of CuI and DMAP in 1:4 molar ratio in a particular solvent at room temperature for 3 hours. The mixture was further kept on standing at room temperature. After 2 days, the pure crystal of complex [Cu(DMAP)<sub>4</sub>]I was isolated in 85% yield. The complex could be isolated only when, DMSO was used as solvent. It was characterized by UV-Vis spectroscopy, FT-IR, ESR analysis, DSC analysis and single crystal XRD. DSC study shows that the compound is stable up to 131 °C. Appearance of a strong peak at 644 nm in UV-Vis spectrum indicates the formation of Cu(II) species. ESR spectrum of the complex shows the presence of X-band, which confirms that copper atom is in +2 oxidation state and the complex has symmetry C<sub>4v</sub>. Structure of the complex was determined by single crystal X-ray diffraction studies. Crystallographic cif files (CCDC Nos. 1040412) are available at www.ccdc.cam.ac.uk/. The single crystal X-ray structure indicates that the complex is square pyramidal in shape, where all the four equatorial positions are occupied by DMAP ligands and one iodine atom in axial position. Another iodine atom was found to be in free-state which resides outside of the coordination sphere.



**Figure: 1** Ortep diagram of [Cu(DMAP)<sub>4</sub>]I complex with 50% probability ellipsoid

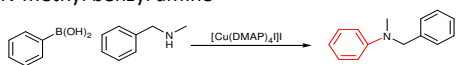
Next, we have carried out an investigation to study the catalytic activity of the synthesized copper complex for Chan-Lam coupling. Initial experiment was carried out by taking phenyl boronic acid and *N*-methyl benzyl amine as model substrate in presence of the copper complex (1 mol%). The reaction was performed by stirring a mixture of phenyl boronic acid (1 mmol), *N*-methyl benzyl amine (1 mmol) and the catalyst (0.001 mmol) in methanol at room temperature (Table 1). The progress of the

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† Supporting Information <sup>1</sup>H-NMR, <sup>13</sup>C-NMR of organic compounds and IR, TGA, DSC, EPR, UV and crystallographic data of the Cu-complex. These data are available free of charge via the Internet. See DOI: 10.1039/x0xx00000x

reaction was monitored by using TLC. After 15 min of reaction, the reaction produced the desired coupling product in 69% yield. Thereafter, the reaction was studied by increasing the catalyst amount to 2 mol%. To our surprise, the reaction was over just in 5 min with excellent yield of 93%. Further increase of catalyst amount to 4 mol% could not improve the result to a better extent. The study was further carried out using different solvents such as ethanol, water, DMSO etc. Interestingly, the reaction also proceeds quite efficiently in water at room temperature in 1h with 86% yield of the desired product (Table 1, entry 5). Finally, the use of 2 mol% of the Cu-complex and equimolar amount of the substrates in methanol was considered as the optimum condition for the reaction at room temperature.

**Table 1.** Optimization experiments for coupling of phenyl boronic acid and N-methyl benzyl amine

|  |                       |                  |            |                        |
|---|-----------------------|------------------|------------|------------------------|
| Entry   | [Cu(DMAP)4]I (Mole %) | Solvent (2 mL)   | Time (Min) | Yield <sup>b</sup> (%) |
| 1   | 1                     | MeOH             | 15         | 69                     |
| 2   | 2                     | MeOH             | 5          | 93                     |
| 3   | 4                     | MeOH             | 5          | 95                     |
| 4   | 2                     | EtOH             | 8          | 85                     |
| 5   | 2                     | H <sub>2</sub> O | 60         | 83                     |
| 6   | 2                     | MeCN             | 20         | 70                     |
| 7   | 2                     | DMSO             | 150        | 17                     |

<sup>a</sup>Reaction condition: Phenylboronic acid (1 mmol), N-methylbenzylamine (1 mmol) solvent (2 mL), rt; <sup>b</sup>.Isolated Yield.

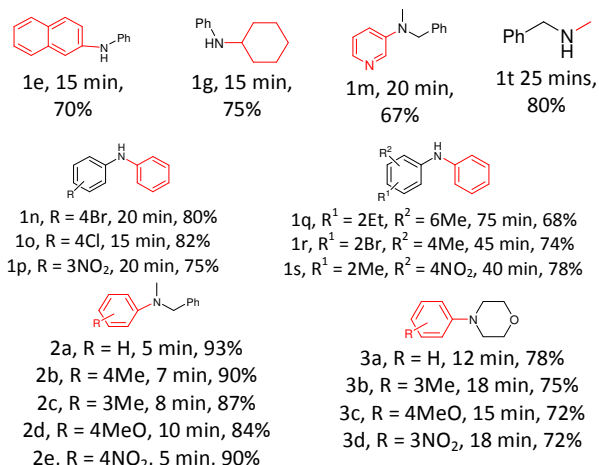
After optimizing the reaction condition, the reaction was extended to various primary and secondary amines and different boronic acids. Results are summarized in Table 2. In all the cases the reaction is very rapid and the yields of the products are also very high. It has been observed that the presence of an electron withdrawing substituent in boronic acid increases the reaction rate. On the other hand, enhancement of product yield was observed in case of amines bearing electron pumping group. The reaction also works well in case of methyl boronic acid. Reaction of methyl boronic acid with benzyl amine resulted in the formation of corresponding N-methyl benzyl amine in 80 % yield after 25 min of reaction at room temperature in methanol (Table 2, entry 1t). Secondary amines such as N-methyl benzyl amine, morpholine etc could also be converted to respective N-arylated product in high yield. However, in case of morpholine, 1.2 equivalent of boronic acid was used to improve the yield.

**Table 2.** Chan-Lam coupling of various amine with different boronic acids<sup>a</sup>

$$\text{R}^1\text{-B(OH)}_2 + \text{R}^2\text{-N(R}^3\text{)} \xrightarrow[\text{MeOH}]{[\text{Cu(DMAP)}_4]\text{I}} \text{R}^1\text{-N(R}^2\text{)(R}^3\text{)}$$

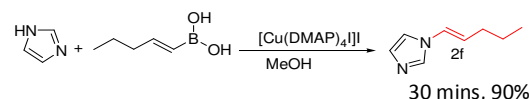
1a, R = H, 10 min, 87%  
 1b, R = 4MeO, 15 min, 81%  
 1c, R = 3Me, 15 min, 82%  
 1d, R = 4Me, 12 min, 85%  
 1f, R = 4NO<sub>2</sub>, 10 min, 88%

1h, R = H, 10 min, 83%  
 1i, R = 3Me, 16 min, 81%  
 1j, R = 4Me, 18 min, 80%  
 1k, R = 4NO<sub>2</sub>, 8 min, 83%  
 1l, R = 3 NO<sub>2</sub>, 11 min, 78%



<sup>a</sup>Reaction condition: amine (1 mmol) boronic acid (1 mmol) MeOH (2 mL) and [Cu(DMAP)<sub>4</sub>]I (2 mol%); isolated yield. <sup>b</sup>1.2 mmol of boronic acid was used.

We have also examined the efficacy of the catalyst for alkenyl boronic acid. When 1-pentenyl boronic acid is treated with imidazole under the same reaction condition at room temperature, corresponding enamine was isolated in 90% yield after 30 min of reaction (Scheme 2).



**Scheme 2**

Thereafter, the C-N coupling reaction was extended for various amides under the same reaction condition (Table 3). In all the cases, the method produces high yield of the product within considerably shorter reaction time. However, the rate of reaction was found to be slower than that for amines with slightly lower yield of the product.

**Table 3.** Chan-Lam reaction of amide with boronic acids

General reaction scheme: An aryl boronic acid ( $R^1\text{-B(OH)}_2$ ) reacts with an amide ( $R^2\text{-NH-C(=O)-R}^3$ ) in the presence of  $[\text{Cu}(\text{DMAP})_4]\text{I}$  in MeOH to form an aryl amide ( $R^1\text{-NH-C(=O)-R}^3$ ).

Chemical structure of intermediate 4a:  $R = 3\text{Me-Ph}$ , 30 min, 75%.

4a,  $R = 3\text{Me-Ph}$ , 30 min, 75%

4b,  $R = 4\text{Cl-Ph}$ , 35 min, 75%

4c,  $R = \text{Ph}$ , 25 min, 78%

4e,  $R = 2\text{-naphthyl}$ , 45 min, 69%

4h,  $R = 3\text{NO}_2\text{-Ph}$ , 25 min, 80%

4i,  $R = 4\text{NO}_2\text{-Ph}$ , 25 min, 80%

Chemical structure of intermediate 4d:  $R = \text{Ph}$ , 38 min, 72%.

4d,  $R = \text{Ph}$ , 38 min, 72%

4f,  $R = 2\text{-Naphthyl}$ , 55min, 65%

4g,  $R = 4\text{F-Ph}$ , 35 min, 75%

<sup>a</sup>Reaction condition: amide (1 mmol) boronic acid (1 mmol) MeOH (2 mL) and [Cu(DMAP)<sub>4</sub>]I (2 mol%); isolated yield

Next, the scope for the C-N bond forming reactions was examined using tosyl azide under the same reaction condition. Results are summarized in Table 4. Under the same reaction condition, yield of the products were found to be relatively low.

**Table 4.** Chan-Lam reaction of tosylazide with boronic acids

<sup>a</sup>Reaction condition: azide (1 mmol) boronic acid (1 mmol) MeOH (2 mL) and [Cu(DMAP)<sub>4</sub>]I (2 mol%); isolated yield

After successful application of our catalyst for C-N bond forming reactions, the method was further extended for C-S bond forming reactions. The process was examined for coupling reaction of different thiols with boronic acid in methanol in presence of copper complex under the same reaction condition (Table 5). The copper complex is also very effective in catalyzing C-S cross coupling reaction, though the reaction time is somewhat more compared to that of amines. In this case, the thiols with an electron withdrawing group increase the rate of the reaction as well as yield of the product.

**Table 5.** Reaction of thiols with boronic acids

|   |   |  |
|---|---|--|
| 5a, R <sub>1</sub> = H, R <sub>2</sub> = H, 40 min, 80%     | 5b, R <sub>1</sub> = H, R <sub>2</sub> = 4MeO, 50 min, 78%                | 5c, R <sub>1</sub> = H, R <sub>2</sub> = 4NO <sub>2</sub> , 35 min, 85%    |
| 5d, R <sub>1</sub> = H, R <sub>2</sub> = 4Br, 40 min, 80%   | 5e, R <sub>1</sub> = 4MeO, R <sub>2</sub> = 4MeO, 55 min, 76%             | 5f, R <sub>1</sub> = 4MeO, R <sub>2</sub> = 4NO <sub>2</sub> , 50 min, 81% |
| 5g, R <sub>1</sub> = 4Me, R <sub>2</sub> = 4Br, 65 min, 80% | 5h, R <sub>1</sub> = 4Br, R <sub>2</sub> = 4NO <sub>2</sub> , 50 min, 83% | 5i, R <sub>1</sub> = 4Br, R <sub>2</sub> = H, 55 min, 78%                  |

<sup>a</sup>Reaction condition: thiol (1 mmol) boronic acid (1 mmol) MeOH (2 mL) and [Cu(DMAP)<sub>4</sub>]I (2 mol%); isolated yield.

The single crystal XRD study shows that the catalyst is square pyramidal in shape with five coordination number and has a vacant co-ordination site. It could be clearly visualized from the X-ray structure that one iodine atom is situating away from the central copper atom. Hence, the formation of the intermediate transmetalated species via displacement of the loosely bound iodine ligand is much more facile in this case. This could be the reason for acceleration of the reaction rate of the Chan-Lam cross coupling reaction.

## Conclusions

In conclusion, we have developed a novel copper catalyst for an improved Chan-Lam protocol for C-N and C-S bond forming reactions. This new protocol is simple and rapid, which can be performed at room temperature producing the coupling product within a short time. The catalyst could be used very effectively for coupling reaction of amines, amides and thiols with boronic acids to produce corresponding coupling products in high yield.

Financial Support from DST, India (Grant No. SR/S1/OC-43/2011) is gratefully acknowledged. SR thanks UGC, India for a fellowship

under RFMS scheme and BK thanks CSIR for senior research fellowship.

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