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# "On Water" promoted *N*-arylation reactions using Cu (0)/myo-inositol catalytic system

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ABSTRACT

Myo-inositol is originally applied as a cardiovascular medicine in clinic, which can be multi-ton manufactured *via* extraction from the byproducts in agricultural product processing such as defatted rice bran and corn-soaking water. Herein, the application of myo-inositol (MI) as a novel versatile tridentate *O*-donor ligand has been first described for promoting Cu-catalyzed amination reaction in aqueous medium.



## Introduction

Arylamines structural fragments are well favorable for the druglikeness or drugscore [1], including antifungal drug (Itraconazole) [2a], anti-inflammatory medicine (Diclofenac acid [2b], Mefenamic acid [2c]), rheumatoid arthritis drug (Tofacitinib [2d]) and anticancer agent (Dasatinib [2e], Imatinib [2f]). The general synthetic protocols for these challenging molecules are usually depending on using highly activated aryl halides ($S_NAr$ reaction) [3], Ullmann-type coupling reaction [4], or Buchwald-Hartwig reaction [5]. Copper catalyst- featured by inexpensive and low toxicity -is shown to offer expedited access to C—N coupling products by amination is getting more and more attention. Earlier, Buchwald [6] and Taillefer [7] overcame the drawbacks of classical Cu-mediated Ullmann-type coupling reaction, such as high catalyst loading, high-boiling solvent, long reaction time, severe temperature, narrow substrate and erratic yield, by adding chelating ligand in the reaction. By then, copper accompanying with auxiliary multidentate chelating ligands have been extensively demonstrated to facilitate amination [4b,4c]. Although polar aprotic solvents, such as DMSO, DMF and NMP, are generally essential to make most ligands working in homogeneous system, it imped their industrial development because these high boiling point solvents generally suffer from recovery issue.

As green chemistry is acquiring an increasingly important role, reactions in aqueous media are of great interest for large-scale industrial processes. Investigations regarding Ullmann reactions in water are increasingly performed over the past two decades [8]. However, limitations of these methods are that only with aryl halides bearing *ortho*-carboxy [8f,8g] or water-soluble amine [8a,8d,8h] the reaction could take smoothly place in water. Moreover, the additional assistance of microwave radiation is required; it seriously hampers its extensive application [8e]. These issues in stability, reactivity of the catalyst and solubility of substrate hitherto remain a significant challenge for assembly of arylamines via the coupling reaction in water.

In 2006, Chen initially proposed the usage of 1,1,1-tris-(hydroxymethyl)ethane (**L1**, Fig. 1) as a *O*-donor tridentate-tripod ligand for Cu-catalyzed carbon-heteroatom bond formation [9]. Using **L1** as a lead ligand, myo-inositol (MI) was successfully screened as a tridentate-tripod ligand to access C—N coupling aminated products in aqueous phase (Fig. 1). We speculated that MI may display better chelating capability than **L1**, because the three hydroxyl groups are restricted to maintain preferred chelating conformation by immobilizing on a ring. Additionally, the hydroxyl groups are benefit to enhance the solubility of intermediate cuprate species in water. Notably, MI is directly applied as a cardiovascular drug in clinic, and also used as an important synthetic intermediate in the preparation of drugs (e.g., inositol hexanoate, inositol selenite and fluoroinositol), for the treatment of anxiolytics, depressants and diabetic [10]. Besides, MI could be multi-ton manufactured via extraction from the byproducts in agricultural product processing such as defatted rice bran and corn-soaking water. Herein, we first introduce MI as a new natural ligand and demonstrate its application in the direct amination form aryl halides and various amine sources in aqueous medium.

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0040-4039/

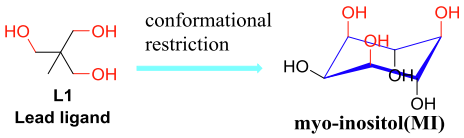


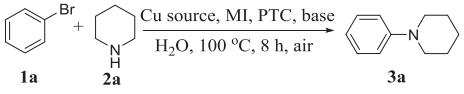

**Fig. 1.** Schematic Diagram Depicting the Procedure for the Discovery of Myo-inositol.

## Results and discussion

To initiate our studies, we treated bromobenzene with piperidine (5.0 equiv) in the presence of 20 mol% Cu-catalyst and MI at 100 °C in a hydrothermal reactor without any inert gas protection (Table 1). Amination product **3a** was obtained in 38% yield under aqueous condition, using copper powder as catalyst (entries 1–4). Interestingly, performing Cu-catalytic amination reaction in dry DMSO, **3a** was not observed (entry 1), suggesting that water was essential. Only trace **3a** was detected without MI, indicating that MI played an important role to promote Cu catalytic capability. Then, attempts to reduce the amounts of amine by using inorganic base and TBAB were successful, which exclusively promoted the conversion of amination product **3a** (90%, entry 5). In addition, lowering the loading of copper powder to 10% delivered **3a** with quantitative yield (entry 6). The use of other base in place of $Cs_2CO_3$ led to lower yield, with $Cs_2CO_3$ proving to be optimal in terms of yield (entries 8–10). In endeavors to improve the reaction, we turned our attention to different PTCs to favor the formation of coupling product in water. Incorporation of TBAB, PEG-400, 18-crown-6 or TBAHS into reaction led to obviously different results, and TBAHS was beneficial and furnished **3a** in 94% isolated yield. In comparison to MI, the lead tridentate ligand **L1** expressed the weaker effect on the transformation (entry 14). Thus, we hypothesized that preferred conformation of three hydroxyls was contributed to facilitate the amination.

With optimized conditions in hand, we set out to evaluate the scope of aryl halides and amines that would participate in this transformation, as shown in Table 2. Gratifyingly, Cu powder/MI-catalyzed C—N coupling reaction of aryl halides with amines gave desired compounds in good to excellent yield (76–97%), which was more potential comparably to results reported in literatures [8d]. Substrates bearing electron-withdrawing groups (**3e**) coupled with better yield than electron-donating substituent (**3c**). The better solubility of the amine in water, it seemed to be delivered the amination product in higher yield (**3q** *vs* **3r**). In addition, electron deficient aryl chlorides furnished the target products in excellent yields (**3l–n**, **3s**), and the presence of carboxyl substituents on the aromatic ring also facilitated the coupling reaction, presumably due to helping to increase water solubility. In spite of an often relatively difficult synthesis and instable property, aminothiophenes have been widely compared to anilines due to their exceptional electronic properties [11]. Through this catalytic system, *o*-iodothiophene could be smoothly converted to aminothiophene **3d** in 90% yield. Moreover, with regard to the sterically hindered acyclic secondary amines, target compounds (e.g. **3k**, 80% yield) could be readily acquired in our case. Interestingly, when the bifunctional compound tryptamine was reacted as substrate, the different results were appeared by changing the loading of bromobenzene. The primary amine preferentially coupled with bromobenzene (1 equiv) giving **3o** in 84% yield; however, the bis-arylation product **3p** was obtained in 91% yield when 2.0 equiv bromobenzene was used. Accordingly, we proposed that coupling

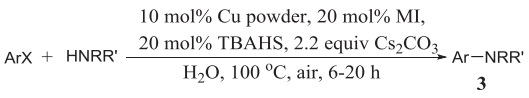
**Table 1**
Identification of Reaction Conditions.[a]

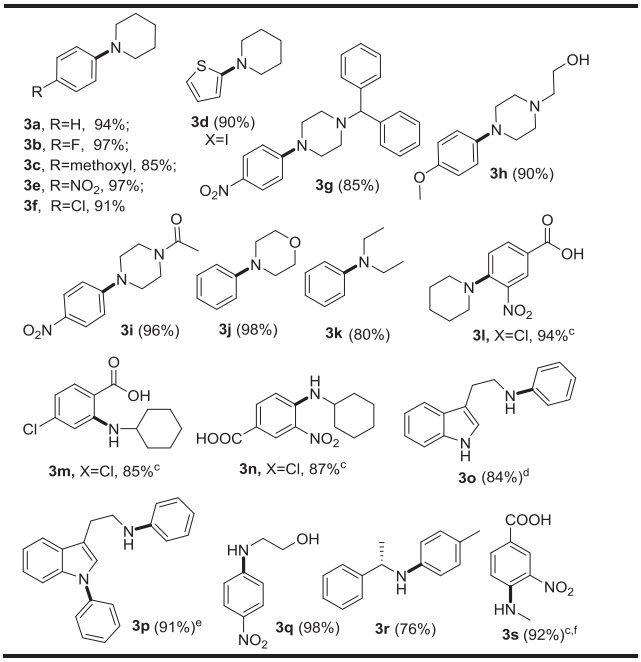



| Entry | Cu (mol%) | Base | PTC (20 mol%) | Yield (%)[b] |
|---|---|---|---|---|
| 1[c] | Cu (20) | – | – | 38/0[d]/trace[e] |
| 2[c] | CuI (20) | – | – | 19 |
| 3[c] | $Cu_2O$ (20) | – | – | 28 |
| 4[c] | $CuSO_4$ (20) | – | – | 0 |
| 5 | Cu (20) | $Cs_2CO_3$ | TBAB | 90 |
| 6 | Cu (10) | $Cs_2CO_3$ | TBAB | 87 |
| 7 | Cu (5) | $Cs_2CO_3$ | TBAB | 65 |
| 8 | Cu (10) | $K_3PO_4{\cdot}3H_2O$ | TBAB | 80 |
| 9 | Cu (10) | KOH | TBAB | trace |
| 10 | Cu (10) | $K_2CO_3$ | TBAB | 86 |
| 11 | Cu (10) | $Cs_2CO_3$ | PEG-400 | 44 |
| 12 | Cu (10) | $Cs_2CO_3$ | 18-Crown-6 | 67 |
| 13 | Cu (10) | $Cs_2CO_3$ | TBAHS | 94 |
| 14[f] | Cu (10) | $Cs_2CO_3$ | TBAHS | 65 |

[a] Standard condition: **1a** (1.0 mmol), **2a** (1.5 mmol), 10 mol% Cu powder, 20 mol% MI, 20 mol% PTC, base (2.2 mmol), $H_2O$ (2.0 mL), 100 °C, 8 h, and the reaction was run in a hydrothermal reactor, unless noted otherwise.
[b] Isolated yield.
[c] **1a** (1.0 mmol), **2a** (5.0 mmol), 20 mol% Cu catalyst.
[d] Dry DMSO as solvent.
[e] Absence of MI.
[f] **L1** was used as ligand instead of MI.

**Table 2**
Cu powder/MI-Catalyzed Coupling Reaction of Aryl halides with Amines in water.[a,b]




[a] Standard condition: aryl bromides (1.0 mmol), amines (1.5 mmol), 10 mol% Cu powder, 20 mol% MI, 20 mol% TBAHS, $Cs_2CO_3$ (2.2 mmol), $H_2O$ (2.0 mL), 100 °C, unless noted otherwise.
[b] Isolated yield.
[c] $Cs_2CO_3$ (3.0 mmol).
[d] Bromobenzene (1.0 mmol), tryptamine (1.0 mmol).
[e] Bromobenzene (2.0 mmol), tryptamine (1.0 mmol).
[f] 40% aqueous methylamine (10.0 mmol).

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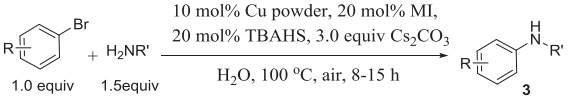
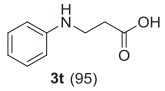
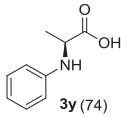
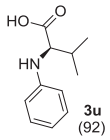
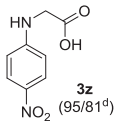
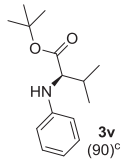
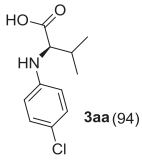
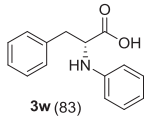
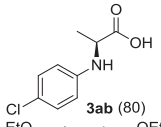
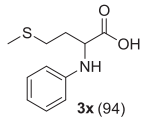
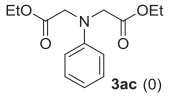
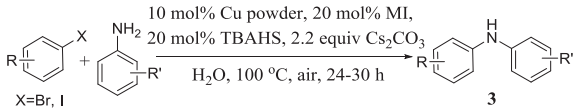
**Table 3**
Cu powder/MI-Catalyzed Coupling Reaction of Aryl bromides with Amino Acids in Water.[a]

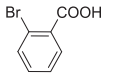
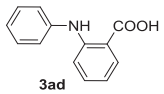
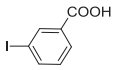
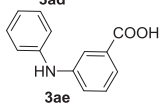
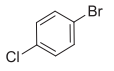
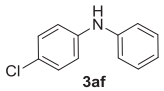
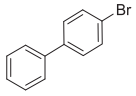
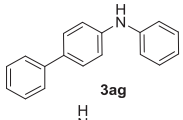
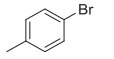
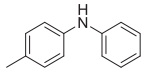
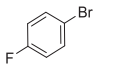
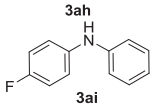
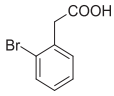
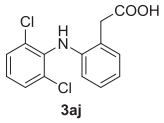



| Entry | Product (yield, %)[b] | Time (h) | Entry | Product (yield, %)[b] | Time (h) |
|---|---|---|---|---|---|
| 1 |  **3t** (95) | 10 | 6 |  **3y** (74) | 10 |
| 2 |  **3u** (92) | 10 | 7 |  **3z** (95/81[d]) | 8 |
| 3 |  **3v** (90)[c] | 10 | 8 |  **3aa** (94) | 10 |
| 4 |  **3w** (83) | 15 | 9 |  **3ab** (80) | 8 |
| 5 |  **3x** (94) | 10 | 10 |  **3ac** (0) | 15 |

[a] Standard condition: aryl bromide (1.0 mmol), amino acids (1.5 mmol), 10 mol% Cu powder, 20 mol% MI, 20 mol% TBAHS, $Cs_2CO_3$ (3.0 mmol), $H_2O$ (2.0 mL), 100 °C, unless noted otherwise.
[b] Isolated yield.
[c] $Cs_2CO_3$ (2.2 mmol).
[d] Without MI.

**Table 4**
Cu Powder/MI-Catalyzed Coupling Reaction of Aryl Halides with Aryl Amines in Water.[a]




| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1[c] |  |  **3ad** | 24 | 93 |
| 2[c] |  |  **3ae** | 24 | 91 |
| 3 |  |  **3af** | 30 | 72 |
| 4 |  |  **3ag** | 30 | 68/89[d] |
| 5 |  |  **3ah** | 30 | 75 |
| 6 |  |  **3ai** | 30 | 79 |
| 7[c] |  |  **3aj** | 30 | 82[e] |

[a] Standard condition: aryl halides (1.0 mmol), aryl amines (1.0 mmol), 10 mol% Cu powder, 20 mol% MI, 20 mol% TBAHS, $Cs_2CO_3$ (2.2 mmol), $H_2O$ (2.0 mL), 100 °C, 8 h, unless noted otherwise.
[b] Isolated yield.
[c] $Cs_2CO_3$ (3.0 equiv).
[d] 50% DMSO as co-solvent.
[e] The loading of 2-(2-bromophenyl)acetic acid was 10 g, and **3aj** was purified by recrystallization from ethanol.

reaction of aryl halides with azoles also could be facilely proceeded catalyzed by Cu/MI system in aqueous medium.

Over the past two decades, the functionalization of amino acids has attracted continuous attention from both academia and industry [12]. Herein, we tried to combine aryl bromides and amino acids by using cooper powder/MI to realize various reactions in water (Table 3). The highly hydrophilic amino acid Gly had capability of transforming to **3z** in 95% yield. Obviously, the reactivity of amino acids seemed to be relative to water solubility; indeed, according to the result that poor water-soluble amino acid of D-Phe was employed, **3w** was prepared in 83% even if reaction time was prolonged (entry 4). Noteworthy was that **3v** was obtained in 90% yield with no detected hydrolyzed product observed (entry 3, Table 3). L-Asp unfortunately afforded undesired decarboxylated products of **3y**, **3ab** in 74%, 80% respectively. Due to the instability of β-carboxy amino acid, we reasoned that amino acids containing β-carboxy were not suitable for this reaction. Further studies revealed that diethyl iminodiacetate did not react under the basic conditions. Given the potential chelating ability of amino acid [13], the reaction was further investigated by control experiment without MI. As evidenced by the example of entry 7, **3z** was formed in 81% yield in the absence of MI. Hence, we speculated that MI and amino acids worked as co-ligands to collaboratively participate in accelerating the arylation of amino acids.

Subsequently, to explore the feasibility of this approach, aromatic amines and different halides were examined as substrates in water, and the results were summarized in Table 4. To our delight, the C—N coupling reactions smoothly proceeded between aryl bromides (iodides) and aryl amines in water, affording products in 68–93% yields. The aromatic amines with carboxyl substituent increased the yield of the coupling product, presumably due to the increased solubility of sodium carboxylate. In these cases, excess amounts of cesium carbonate (3.0 equiv) had often to be used. Amination was occurred by using 4-bromobiphenyl and aniline as reactants, but a lower yield (68%, entry 4) was observed due to their poor water-solubility, although after a prolonged reaction time. The addition of DMSO, a co-solvent that enabled the Cu-catalyzed coupling of 4-bromobiphenyl by forming homogeneous reaction conditions, increased the yield of **3ag** (89%). The scalability of this protocol was tested through preparation of the diclofenac (non-steroidal anti-inflammatory drug) **3aj** on a 10 g scale, directly using 2-bromophenylacetic acid and 2,6-dichloroaniline. In this case, the simple coupling was successfully reduced the waste, compared to traditional synthetic route [14].

Ultimately, to gain insight into the mechanism of cross-coupling reactions, we used the radical clock 1-allyloxy-2-iodobenzene as

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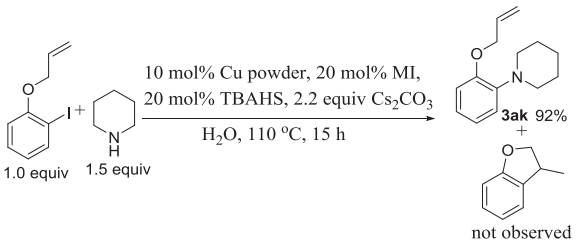


**Scheme 1.** Reaction between 2-(Allyloxy)iodobenzene and Piperidine.

substrate to determine if the aryl halide activation step proceeds *via* radical intermediates [15]. Results revealed that no conversation of ring closure product was observed, with only affording the amination coupling compound **3ak** (Scheme 1). We reasoned that the use of copper powder could be oxidized *in situ* to form active Cu (I) which participated in Cu (I)/Cu (III) catalytic cycle in the presence of water [16].

## Conclusion

In summary, we have developed Cu powder/MI catalytic system enabling rapid access to substituted aryl amines, which represents the first step toward the development of a natural ligand myo-inositol for accelerating coupling reaction in water. The simple reaction conditions, the easy isolations of the products and the broad scope of substrate render this protocol particularly attractive. This reaction allows the conversion of simple starting materials to complex aryl amines structural fragments, which are important synthetic intermediates in the preparation of bioactive molecules such as diclofenac sodium. On the other hand, MI contains multiple chiral centers, which may open a new scope for chiral synthesis of various important optically active aryl amines in cheap and environmentally friendly way. Efforts to apply our Cu/MI-based system to other catalytic reactions and to expand the scope of the aromatic amine to other classes of halides are currently underway in our laboratory.

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## Appendix A. Supplementary data

General information, experimental procedures and copies of $^{1}H$ NMR and $^{13}C$ NMR spectra for all products were placed in supporting information file.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.06.033.

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