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Copper-catalyzed aryl amination in aqueous media with 2-dimethylaminoethanol ligand☆

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Abstract—Copper-catalyzed amination of aryl bromides and iodides under mild conditions has been developed with 2-dimethylaminoethanol as ligand and water as solvent. A variety of hydrophilic and hydrophobic aryl halide substrates have been aminated in good yield with a variety of amino acids, amino alcohols and peptides. This method has successfully *N*-arylated some hydrophilic amino compounds not available by other methods.

Reactions in aqueous media are of great interest for large-scale industrial processes due to the issues of economy and safety.[1] Transition metal-catalyzed reactions in aqueous media have been widely explored.[2] Here, sufficient miscibility of the catalyst in both aqueous phase and organic phase is required.[3] For example, a variety of water-soluble triarylphosphines were designed and applied to applications particularly for palladium catalysts used in Suzuki, Heck and amination reactions.[4] Water-soluble and sterically demanding alkylphosphines have also been applied to Suzuki, Heck and Sonogashira reactions in aqueous media.[5] Attempts have been made to increase the solubility of copper species in organic solvents. Copper(II) pivalate was chosen as a catalyst for coupling between pentavalent organobismuth reagents and amines because of its high solubility in common organic solvents.[6] The phosphazene base P_4-*t*-Bu has successfully promoted CuBr-catalyzed coupling of aryl halides with phenols probably due to the enhanced solubility of CuBr in the presence of P_4-*t*-Bu.[7]

Water was chosen as a solvent for Ullmann condensations to make *p*-phenylenediamine from halobenzenes under traditional conditions in a bomb under high pressure and temperature.[8] In a recent report, water was used as solvent to convert bromopyridine to aminopyridine with Cu_2O catalyst accompanied by 22% of hydroxypyridine byproduct.[9] However, water has rarely been used as a solvent for the recently developed copper-catalyzed aminations under mild conditions, particularly when arylhalides are starting materials.[10] Amino acids and peptides are usually arylated by aromatic nucleophilic reaction or substitution reaction of a protected carboxylic acid and subsequent hydrolysis.[11] Ma et al. have found that amino acids are good ligands to accelerate the Ullmann condensation with an additional amine in DMSO as solvent.[12] The same group reported a successful copper- catalyzed amination between aryl halides and a variety of amino acids in DME and DMF.[13] However, this method appears to be limited to α- and β-amino acids bearing hydrophobic substituents. Amino acids other than α- and β-amino acids failed to give any arylamine products. The β-amino acids are less effective than α- amino acids and highly hydrophilic amino acids such as L-glutamic acid, L-serine and glycine failed to couple at all with aryl halides under these conditions.[14] It was recognized that the low solubility of the highly hydrophilic amino acids in typical organic solvents could be responsible for this failure.[13] This problem was partially alleviated by solubilizing the amino acids as their tetrabutylammonium salts in the dipolar aprotic solvents *N*,*N*-dimethylacetamide and acetonitrile.[15] Using this protocol, moderate yields were reported for the amino acids examined but it is interesting that in this approach water was removed prior to the addition of copper catalyst, even though water is expected to be a good solvent for such substrates.

Keywords: Amination; Copper catalysis; Amino acid.

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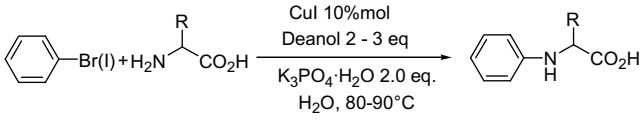
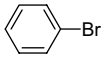
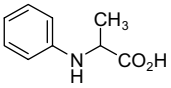
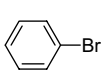
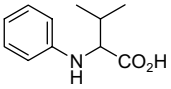
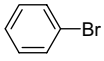
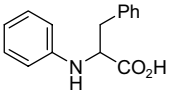
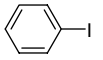
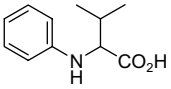
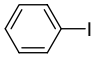
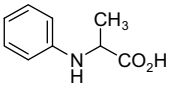
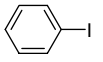
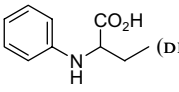
Recently, we reported that 2-dimethylaminoethanol (deanol) is an efficient solvent for the copper-catalyzed amination reaction. In this system the addition of water slows down the reaction yet it has the advantage of suppressing the arylether byproduct from arylation of deanol.[16] This earlier study prompted us to explore the possibility of coupling hydrophilic substrates in aqueous media. Here we demonstrate a copper-catalyzed amination of amino acids and especially those amino acids that have failed to undergo arylation reaction by other methods. Examples include glycine, glutamic acid, non-α- and β-amino acids and amino alcohols and other amines.

In order to systematically evaluate the roles of catalyst precursor, ligand and base the coupling of DL-valine with bromobenzene was examined (Table 1). Control experiments indicate that deanol is essential for this reaction, in part by providing a soluble catalytic species (entry 1). An attempt to use deanol as the only solvent (no water, entry 3) provided only a moderate amination yield and an incomplete conversion of bromobenzene. We also examined ethylene glycol as a ligand instead of deanol (entry 4), and observed significant insoluble components in the reaction mixture. A moderate yield of aryl amino acid and incomplete conversion of bromobenzene was observed. Both glycolic acid and tartaric acid (entries 5 and 6) were proved to be copper solubilizing ligands but were ineffective in this particular reaction. It seems that the solubility of copper species is not the only criteria for this catalytic reaction, as some chelation modes are not catalytically effective. As base, potassium carbonate and sodium phosphate are useful but less effective than potassium phosphate (entries 7 and 8). In contrast, potassium hydroxide (entry 9) gave a low conversion with bromobenzene and only <5% arylamine was isolated. The strongly basic conditions likely impair the stability of copper complex with deanol and degrade the catalytic effect. Copper metal is a superior catalyst precursor for the amination reaction using deanol as solvent,[16] but alone it is much less effective here in the presence of added water (entry 10). Both cupric chloride and cuprous oxide are effective and cuprous oxide has equivalent catalytic effect in regards to isolated yield (entries 11 and 12). However, higher racemization was observed for the reactions with cuprous oxide catalyst than that with CuI as catalyst. Chiral HPLC analysis of the *N*-phenylvaline from L-valine indicated that it contains 1.5% of *N*-phenyl-D-valine and 98.5% of *N*-phenyl-L-valine with CuI as catalyst.

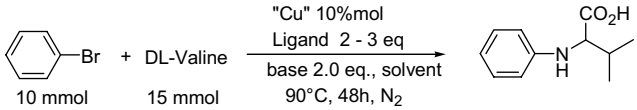
Table 2. Copper-catalyzed coupling of non-polar α-amino acids with bromobenzene and iodobenzene



Entry	ArX	Product	Yield[a] (%)
1		 (DL)	88
2		 (DL, D and L)	90
3		 (DL)	80
4		 (DL)	85
5		 (DL)	82
6		 (DL)	80

[a] Isolated yield.

Table 1. Catalyst, base and ligand optimization study for the amination of bromobenzene with DL-valine in aqueous media



Entry	'Cu'	Ligand	Base	Solvent	Yield[a] (%)
1	CuI	Nil	K_3PO_4	H_2O	<5
2	CuI	Deanol	K_3PO_4	H_2O	90
3	CuI	Deanol	K_3PO_4	Deanol	46
4	CuI	Ethylene glycol	K_3PO_4	H_2O	62
5	CuI	Glycolic acid	K_3PO_4	H_2O	<5
6	CuI	Tartaric acid	K_3PO_4	H_2O	<5
7	CuI	Deanol	K_2CO_3	H_2O	67
8	CuI	Deanol	Na_3PO_4	H_2O	52
9	CuI	Deanol	KOH	H_2O	<5
10	Cu(0)	Deanol	K_3PO_4	H_2O	21
11	$CuCl_2$	Deanol	K_3PO_4	H_2O	73
12	Cu_2O	Deanol	K_3PO_4	H_2O	88

[a] Isolated yield.

But with Cu_2O as catalyst, 18.4% *N*-phenyl-D-valine was observed. The issue of racemization remains to be systematically examined.

Bromobenzene and iodobenzene are both very reactive with α-amino acids bearing a hydrophobic substituent. Valine afforded the best yield of *N*-arylamino acid product and other amino acids with hydrophobic substituents also gave good yields (Table 2).

Encouraged by the successful *N*-arylation of α-amino acids bearing hydrophobic substitutents, we subsequently explored the *N*-arylation reactions of the amino acids that failed to undergo arylation reaction with the currently available transition metal-catalyzed amination reactions.[13] These are the still more hydrophilic α-amino acids such as glutamic acid, glycine and serine and amino acids other than α- and β-amino acids. The results obtained using the deanol–water system are shown in Table 3. We first examined the reaction of glycine, the simplest amino acid, with iodo- and bromobenzene. Iodobenzene is more reactive than bromobenzene and substrates other than α-amino acids hardly react with aryl bromides. Therefore, we only examined iodobenzenes for the couplings with these other amines. The more water-soluble 3-iodobenzoic acid is more reactive (entry 3) and coupling of β-alanine with iodobenzene also afforded a good yield (entry 4). Glutamic acid and serine (entries 5 and 6) are less reactive as the reactions took longer time and the yields dropped to around 30–50%. This is probably related to the coordination of these amino acids to create copper species quite similar to tartaric acid and glycolic acid that are not good ligands for this copper-catalyzed reaction.

Aspartic acid coupled with iodobenzene efficiently, but when the reaction mixture was acidified during workup, CO_2 was evolved and only *N*-phenylalanine was isolated. An attempt to couple iminodiacetic acid with iodobenzene failed (entry 7).

For the first time, to our knowledge, peptides were arylated by a transition metal-catalyzed aryl amination reaction. Glycylglycine and glycyl-L-leucine reacted at the primary amine site with iodobenzene and we obtained 40% and 46% yield of the respective arylation products (entries 8 and 9).

We have also extended this reaction to amino acids other than α- or β-amino acids and other amines including amino alcohols and diamines (Table 4). In contrast to the methods employing DME or DMF as solvent,[13] this reaction in aqueous media provides efficient *N*-arylation for these amines. Reactions between a variety of iodobenzene and amino acids with different alkyl chains are all successful. The more hydrophilic 2-, 3- or 4-iodobenzoic acids afforded better yields and higher reaction rates (entries 3–5) than iodobenzene. Electron rich 3- and 4-iodoanisole reacted well with 6-aminocaproic acid but a lower yield was observed and longer reaction time was required (entries 6 and 7).

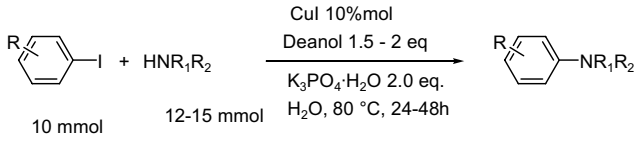
It should be emphasized that an amino acid is not a requirement for this reaction in water as we also have

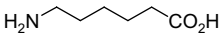
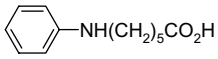
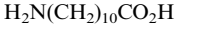
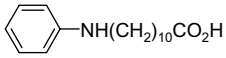
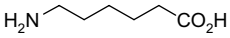
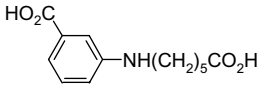
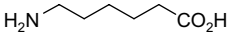
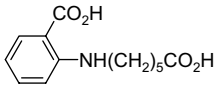
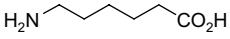
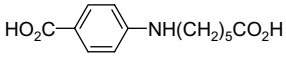
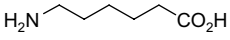
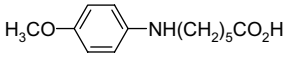
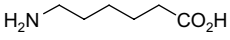
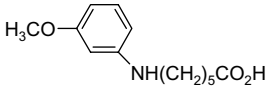
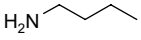
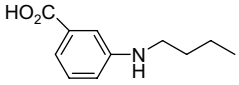
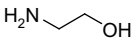
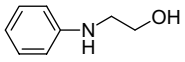
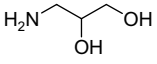
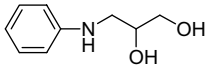
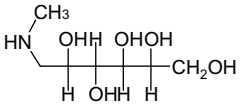
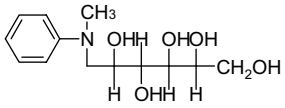
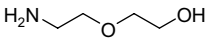
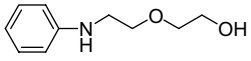
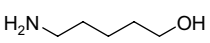
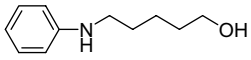
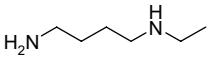
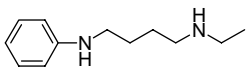
Table 3. Copper-catalyzed amination of ArX with hydrophilic amino acids in water solution (same reaction conditions as in Table 2)

Entry	RNH_2	Product[b]	Yield[a] (%)
1	$HO_2CCH_2NH_2$	HO_2CH_2CHN–	87
2	$HO_2CCH_2NH_2$	HO_2CH_2CHN–	62
3	$HO_2CCH_2NH_2$	HO_2CH_2CHN– (CO_2H)	90
4	HO, O, NH_2	HO, O, H N–	73
5	HO_2C, NH_2, CO_2H	HO_2C, H N–, CO_2H	32
6	HO, NH_2, CO_2H	HO, H N–, CO_2H	49
7	HO_2C, HO_2C, NH	HO_2C, HO_2C, N–	0
8	HO_2C, N H, O, NH_2	HO_2C, N H, O, H N–	40
9	CO_2H, $NHCOCH_2NH_2$	CO_2H, $NHCOCH_2NH$–	46

[a] Isolated yield.
[b] All ArX are iodobenzene except entry 2 is bromobenzene and entry 3 is 3-iodobenzoic acid.

Table 4. Coupling of iodobenzenes with non-α- and β-amino acids and other amines in aqueous media



Entry	Amine	Product[b]	Yield[a] (%)
1			76
2			87
3			92
4			90
5			88
6			46
7			73
8			84
9			90
10			92
11			31
12			77
13			81
14			61

[a] Isolated yield.
[b] All ArX are iodobenzene except entries 3 and 8 are 3-iodobenzoicacid; entry 4, is 2-iodobenzoic acid, entry 5 is 4-benzoic acid, entry 6 is 4-iodoanisole and entry 7 is 3-iodoanisole.

extended this method to other hydrophilic amines including amino alcohols and diamines. 3-Iodobenzoic acid coupled with the simple *n*-butylamine in high yield (entry 8). Job and Buchwald have observed the acceleration effect of the 2-hydroxy functionality to the copper-catalyzed arylation of amino alcohols in a study of

arylation of β-amino alcohols in DMSO/H_2O (2:1) solvent system.[17] Amino alcohols (entry 9) with a 2-hydroxyl group are quite reactive in aqueous solution. Multiple hydroxyl groups in amino alcohols can expedite the reaction (entry 10). Even secondary amines with multiple hydroxyl functionality coupled to iodobenzene in moderate yield (entry 11). The scope of this reaction is not limited to amines with 2-hydroxy groups. We have found that this method could be extended to non-β-amino alcohols and diamines such as 5-hydroxylpentylamine and 2-(2-aminoethoxy)-ethanol which have been coupled with iodobenzene under the same conditions (entries 12 and 13). In a molecule containing both primary and secondary amine the primary amine reacts preferentially (entry 14).

In conclusion, a copper-catalyzed amination of aryl halides under mild conditions in water has been developed with 2-dimethylaminoethanol as ligand. Cu_2O, $CuCl_2$ and $Cu(OAc)_2$ are effective catalysts but CuI afforded the best results. K_3PO_4 works best as base while other bases such as K_2CO_3 and Na_3PO_4 are also effective. Amino acids including α- and β-amino acids with or especially without hydrophobic substituents non-α- and β-amino acids, amino alcohols, peptides and other amines have been aminated. Both aryl iodides and bromides react readily with α-amino acids with hydrophobic substituents while for other amines only aryl iodides provided good yields.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.027. Supplementary material is available for general synthetic methodology, spectroscopic properties and for chiral HPLC analysis of D-, L- and DL-*N*-phenylvaline obtained from the coupling reactions.

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