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Amino acid-mediated Goldberg reactions between amides and aryl iodides

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Abstract—A highly general, experimentally simple, and inexpensive catalyst system was developed for the amidation of aryl iodides by using 5 mol% of CuI as catalyst, 20 mol% of an amino acid as ligand, and K_3PO_4 as base.

Transition metal-catalyzed amide arylation is a widely utilized reaction in academic and industrial laboratories and therefore, has been a focus of interest recently.[1] So far significant improvements have been achieved in Pd-catalyzed amide arylation reactions,[2] but it remains hard to apply these reactions to large and industrial scale syntheses due to the high cost of Pd and the difficulty in removing Pd residues from polar reaction products.

An alternative method for amide arylation is the Cu-catalyzed Goldberg reaction.[3] This method is attractive from an economic standpoint because Cu is much cheaper than Pd. Despite this advantage, the Goldberg reaction is not a popular reaction in organic chemistry due to the necessity to use temperatures as high as 210 °C, highly polar aprotic solvents, strong bases such as alkoxides and NaH, large amounts of the nucleophile, and often large amounts of Cu reagents.

An interesting recent finding is that the Goldberg amidation reaction can be greatly facilitated by certain organic ligands.[4] Similar promotion effects have also been reported lately for other Cu-catalyzed coupling reactions.[5] These findings have given rise to a resurgence in interest in developing mild synthetic methods using Cu-based catalysts as an alternative to Pd catalysts for the formation of aryl–carbon and aryl–heteroatom bonds.

Up to now, the ligands that have been found to promote the Cu-catalyzed aryl–heteroatom coupling reactions include thiophene-2-carboxylate,[6] diamines,[7] 2,2,6,6-tetramethyl-heptane-3,5-dione,[8] 1,10-phenanthroline,[9] *o*-hydroxy-biphenyl,[10] and neocuproine.[11] A special group of ligands, the amino acids, were found to accelerate the Cu-catalyzed coupling reactions between aryl halides and themselves.[12]

It was originally proposed that the Cu–amino acid chelation effect, which may trigger an intramolecular coupling, was the cause of the observed acceleration.[13] However, it was reported very recently by Ma et al. that amino acids can also serve as ligands for the coupling reactions of other nucleophile instead of themselves.[14] Encouraged by this report, we recently initiated a systematic study on the application of amino acids as ligands to Cu-catalyzed cross-coupling reactions. In the present paper, we wish to report our results concerning the Cu-catalyzed amidation reactions.

In the first stage of the study we focused on the coupling between caprolactam and iodobenzene using glycine as the ligand. We examined the effects of various copper salts, bases, solvents, reaction temperatures, and reaction times on the yields of the coupling. The detailed results are listed in Table 1.

As shown in Table 1, we found that the yield of the CuI/glycine-catalyzed amidation reaction is highly dependent on the base. Cs_2CO_3 surprisingly gives the lowest

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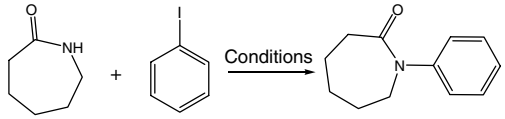
Table 1. Yields of the coupling reaction between caprolactam and iodobenzene under different conditions



Entry	Cu salt[b]	Base	Ligand[c]	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	CuI	CaO	Glycine	Dioxane	100	24	58
2	CuI	NaH	Glycine	Dioxane	100	24	85
3	CuI	Cs_2CO_3	Glycine	Dioxane	100	24	13
4	CuI	K_2CO_3	Glycine	Dioxane	100	24	41
5	CuI	K_3PO_4	Glycine	Dioxane	100	24	97
6	CuI	K_3PO_4	Glycine	Dioxane	100	12	70
7	CuI	K_3PO_4	Glycine	DMF	120	24	98
8	CuI	K_3PO_4	Glycine	THF	70	24	76
9	Cu_2O	K_3PO_4	Glycine	Dioxane	100	24	79
10	$CuCl_2$	K_3PO_4	Glycine	Dioxane	100	24	8
11	$CuSO_4$	K_3PO_4	Glycine	Dioxane	100	24	70
12	CuI	K_3PO_4	Ethylenediamine	Dioxane	100	24	95
13	CuI	K_3PO_4	Glycol	Dioxane	100	24	90
14	CuI	K_3PO_4	2,2′-Bipyridine	Dioxane	100	24	81
15	CuI	K_3PO_4	*N*-Methyl glycine	Dioxane	100	24	98
16	CuI	K_3PO_4	*N*,*N*-Dimethyl glycine	Dioxane	100	24	79
17	CuI	K_3PO_4	Glycine hexyl ester	Dioxane	100	24	95

[a] Isolated yield.
[b] 5 mol%.
[c] 20 mol%.

yield (13%) while CaO and K_2CO_3 also give low yields. NaH gives a fairly good yield (85%) and K_3PO_4 gives the best yield (97%).

Dioxane is a good solvent for the amidation reaction. Use of DMF as solvent also gives a high yield (98%), but the high boiling point of DMF is disadvantageous. Use of THF as solvent, however, gives a relatively low yield (76%).

In addition to CuI, we also used Cu_2O, $CuCl_2$, and $CuSO_4$ as the catalyst. However, the yields with the latter three copper catalysts are much lower than the yield with CuI. Therefore, we conclude that the air stable and inexpensive CuI is the most desirable catalyst.

Compared to glycine ligand, use of ethylenediamine as ligand also gives a good yield of 95%, which is in agreement with Buchwald's studies.[4j] Use of glycol or 2,2′-bipyridine as ligand gives a relatively low yield. Interestingly, it is found that *N*-methyl glycine and glycine hexyl ester can also mediate the amidation reaction very well (yield = 98% and 95%). Nevertheless, *N*,*N*-dimethyl glycine is much less effective (yield = 79%) possibly due to the steric problems.

On the basis of the above results, we conclude that CuI (5 mol%)/glycine (20 mol%)/K_3PO_4/dioxane is a very good catalyst system for the amidation reactions.[14] Although the yield of this newly developed reaction is similar to that reported before with other type of ligands (e.g., diamines),[4] the amino acid-mediated coupling reaction is of interest because of the following reasons. (1) The amino acid is cheap and safe to user. (2) The amino acid ligand is easy to remove after the reaction because it is highly soluble in water. (3) Amino acid waste is relatively environmentally benign. (4) There are a large number of different amino acids. Most of them are chiral and we may use them as ligands in the synthesis of atropisomeric amides.

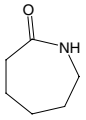
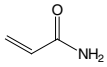
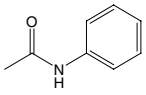
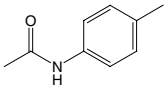
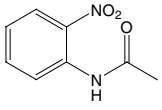
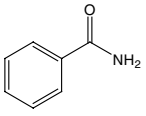
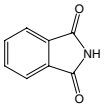
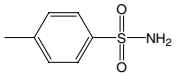
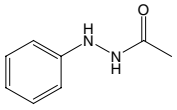
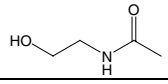
Using the reaction procedure for glycine, we also examined other amino acids as ligands for the amidation reaction (see Table 2). It is found that in addition to glycine, one can also use cystine, cysteine, lysine, arginine, α-alanine, and β-alanine. They all give quite similar yields regardless of the properties of the side chains. It is worthy mentioning that in all the amino acid-

Table 2. Yields of the CuI-catalyzed coupling reactions between iodobenzene and caprolactam or acetanilide with various amino acids as ligands (base = K_3PO_4, solvent = dioxane, temperature = 100 °C, reaction time = 24 h)

Entry	Amide	Amino acid	Yield (%)[a]
1	Caprolactam	Glycine	97
2	Caprolactam	Cystine	92
3	Caprolactam	Lysine	99
4	Caprolactam	α-Alanine	98
5	Caprolactam	Arginine	97
6	Caprolactam	Cysteine	97
7	Caprolactam	β-Alanine	99
8	Acetanilide	Glycine	84
9	Acetanilide	Cystine	88
10	Acetanilide	Lysine	84
11	Acetanilide	α-Alanine	87
12	Acetanilide	Arginine	89
13	Acetanilide	Cysteine	86
14	Acetanilide	β-Alanine	87

[a] Isolated yield.

Table 3. Yields of the CuI-catalyzed coupling reactions between iodobenzene and various amides (base = K_3PO_4, solvent = dioxane, temperature = 100 °C, reaction time = 24 h)

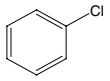
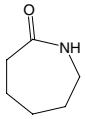
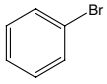
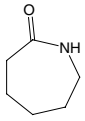
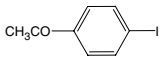
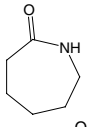
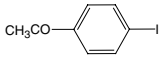
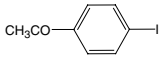
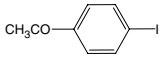
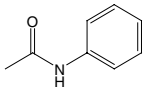
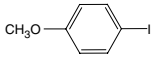
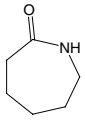
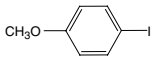
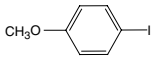
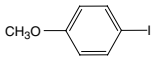
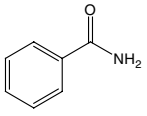
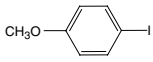
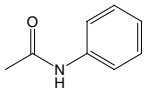
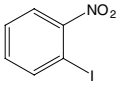
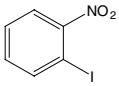
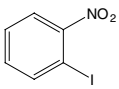
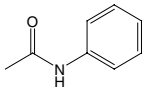
Entry	Amide	Yield (%)[a]		
		Glycine	L-Arginine	β-Alanine
1		97	97	98
2		95	99	95
3		Polymers	Polymers	Polymers
4		84	89	87
5		74	76	78
6		75	79	66
7		97	99	97
8		53	55	55
9		98	97	98
10		80	83	83
11		91	81	98
12		64[b]	63	68

[a] Isolated yield.
[b] *N*-Arylation versus *O*-arylation = 15:1 (GC–MS).

mediated amidation reactions the coupling between iodobenzene and the thiol or amino groups on the amino acid moiety is negligible as tested by GC/MS.

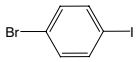
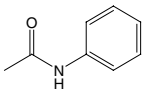
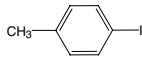
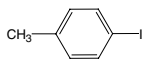
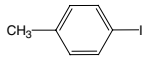
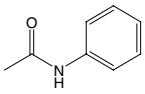
Using glycine, L-arginine, and β-alanine as ligands, we examined the coupling reactions between iodobenzene and various primary and secondary amides (see Table 3). It is found that all the alkyl and aryl amides give high to excellent yields except for one substrate, acrylamide. It appears that in this particular case the amino group of amino acid does a 1,4-addition to acrylamide resulting in the anionic polymerization.

Table 4. Yields of the CuI-catalyzed coupling reactions between various aryl halides and amides (ligand = glycine, base = K_3PO_4, solvent = dioxane, temperature = 100 °C, reaction time = 24 h)

Entry	Aryl halide	Amide	Yield (%)[a]
1			26
2			62
3			98
4			98
5			95
6			84
7			92
8			95
9			90
10			71
11			88
12			98
13			95
14			86
15			91
16			93

(*continued on next page*)

Table 4 (*continued*)

Entry	Aryl halide	Amide	Yield (%)[a]
17			80
18			92
19			95
20			82

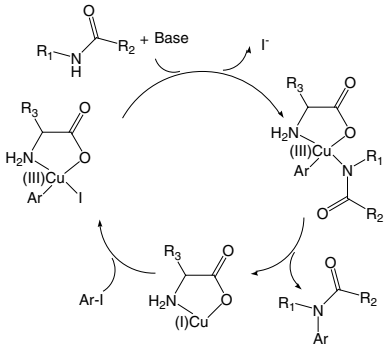
[a] Isolated yield.

Interestingly, an imide (entry 8) can also participate in the coupling reaction, although the yield is relatively low (yield $\approx$ 55%). On the other hand, sulfonamide (entry 10) works fairly well in the amino acid-mediated coupling reaction (yield $\approx$ 83%). Hydrazide (entry 11) gives a very good yield in the coupling (yield = 98% with β-alanine) and the coupling occurs nearly completely at the amide nitrogen as demonstrated by NMR. Moreover, in the coupling of *N*-(2-hydroxy-ethyl)-acetamide, the *N*-arylation versus *O*-arylation ratio is 15:1 as revealed by GC/MS.

Finally, using glycine as ligand we examined the coupling reactions between various aryl halides and amides (see Table 4). It is found that chlorobenzene gives a very low yield of 26% in the coupling. Bromobenzene gives a modest yield of 62%, which is still much lower than the yield seen with iodobenzene (97%).

For aryl iodides, it is found that a variety of substituents at either *ortho*, *meta*, or *para* positions can be tolerated in the amino acid-mediated amidation reaction. In particular, electron-rich aryl iodide (e.g., entries 7–11) works fairly well in the coupling. An aryl iodide with *ortho* substituent (entries 12–14) is also not a problem with the CuI/glycine catalyst. Compared to these Cu-catalysis results, amidation of electron-rich or *ortho*-substituted aryl halides is often difficult with the Pd catalyst.[1,2]

At present the mechanism of the Cu(I) catalyzed coupling reaction is not completely clear yet.[15] Nonetheless, the results from the present study are consistent with the mechanism in which a four-coordinated Cu(III) intermediate is involved (see Scheme 1).[15] According to the mechanism, the role of amino acid ligand in the reaction is either to promote the oxidative addition of ArI to the Cu(I) species or to stabilize the Cu(III) intermediate. The mechanism also explains why it is not the amino group of amino acid ligand but the amide nitrogen that participates in the coupling, because in the Cu(III) complex amide nitrogen is anionic (and therefore, more reactive) whereas the NH_2 group of the amino acid ligand is neutral.



Scheme 1.

In summary, amino acids have been found to be excellent ligands for Cu-catalyzed amidation reactions. The catalyst system is general, inexpensive, safe, and environmentally benign. Efforts to expand the utility of the method to other types of Cu-catalyzed reactions in combination with mechanistic studies are in progress in our group.

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14. Typical procedures for the CuI/amino acid catalyzed amidation reactions are as follows: An over-dried three-neck flask was charged with CuI (47.6 mg 0.25 mmol 5.0 mol %) amide (6.0 mmol) glycine (75.1 mg 1.0 mmol 20 mol %), and K_3PO_4 (2.65 g 12.5 mmol). The flask was filled with nitrogen and aryl iodide (5.0 mmol) was added then. Dioxane (10.0 mL) was added under nitrogen. The reaction mixture was refluxed for 24 h at 100 °C. The resulting suspension was cooled to room temperature and filtered through a pad of silica gel with the help of 100 mL of ethyl acetate. The filtrate was concentrated and the residue was purified by chromatography to afford the pure product.
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