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# Synthesis of Chiral Amino Acid Anilides by Ligand-Free Copper-Catalyzed Selective *N*-Arylation of Amino Acid Amides

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**Abstract:** An atom-economic, practical and cost-effective protocol for synthesis of chiral amino acid anilides *via* ligand-free copper-catalyzed selective C–N cross coupling of chiral amino acid amides and aryl halides, hetereoaryl halides and a vinyl bromide has been developed. No racemization occurred during the C–N coupling. A plausible mechanism is proposed.

**Keywords:** amino acid amides; amino acid anilides; chiral pool; copper; cross-coupling

Chiral amino acid anilides are a subclass of amino acid derivatives and have extensive and important applications. They are essential core structures in a number of bioactive compounds,[1] such as clinical antiarrythmic agent tocainide,[1a] histone deacetylases (HDACs) inhibitors,[1b] pH-controlled light-activated reagents for cancer therapy,[1c] cold menthol receptor antagonists,[1d] and antimalarial agents.[1e] Chiral amino acid anilides are also found as chiral ligands[2] used in catalytic asymmetric Mannich-type reactions,[2a] ruthenium(II)-catalyzed asymmetric transfer hydrogenation of ketones[2b,c] and chiral organocatalysts for asymmetric aldol reactions.[3] Besides, they are used as organic synthesis intermediates[4] and utilized in the synthesis of peptides and peptidomimetics.[5]

Chiral amino acid anilides are typically synthesized *via* three-step synthetic routes. The first step is protection of L-, D- and DL-amino acids with CbzCl,[2c,6] $Boc_2O$,[1b,4b,d,7] phthalic anhydride[8] or ethyl thioltrifluoroacetate.[9] The second step is condensation of *N*-protected amino acids and anilines in the presence of carboxylic activating agents. The last step is removal of the protecting groups to furnish the chiral amino acid anilides. In addition, phenylalanine anilide was synthesized *via* hydrolysis of the optically active β-lactam obtained from a chiral auxiliary-mediated asymmetric induction.[10] All of these approaches involve multiple step synthetic routes, thus resulting in low atom economy, high cost, tedious work-up and potential environmental pollution.

As to the synthesis of racemic amino acid anilides, there are some other methods,[11] but they need multistep synthetic routes or sometimes rare reactants.

Since chiral amino acid anilides are a type of basic and important compound extensively used in medicinal chemical synthesis, chiral catalysis and organic synthesis, there is an important need to search for an efficient, atom-economic, inexpensive synthetic protocol of chiral amino acid anilides.

Based on Corey's anti-synthetic analysis of the molecular structures, direct disconnection the C–N bond of chiral amino acid anilides gives chiral amino acid amides and aryl halides, which means C–N cross-coupling is another potential method for their synthesis.

But there are two amino groups in an amino acid amide molecule, so control of the selective C–N cross coupling of these compounds is unavoidable. To the best of our knowledge, there is no report about control of the selective C–N cross-coupling of chiral amino acid amides and aryl halides to synthesize chiral amino acid anilides. Related to this, Cesati III reported the copper-catalyzed C–N coupling of amino acid amides and protected amino acid amides and vinyl iodides to synthesize amino acid-derived enamides.[13] And Buchwald reported the selective C–N cross-coupling of aniline amino groups and aromatic amides of *ortho*-, *meta*- and *para*-aminobenzamides.[14]

Chiral α-amino acid amides (i.e., 2-alkyl-2-amino acetamides) with aliphatic amino groups and amide amino groups in the specific steric structure are different from these substrates investigated by Buchwald. Given the versatility of palladium catalysts and our experience of palladium-catalyzed C–N cross-cou-

pling,[15] firstly we tried the palladium-catalyzed C–N cross-coupling of phenylalaninamide and bromobenzene under various reaction conditions, but only starting materials were recovered. The reason perhaps is that formation of the especially stable five-member palladium-diamino complex, whose analogues are reported as being very stable,[16] prevents the formation of the C–N bond from bromobenzene and phenylalaninamide.

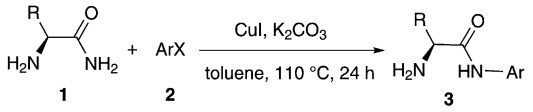
Copper-catalyzed Ullmann-type C–N coupling has a history of more than one hundred years, and as a cost-effective and versatile C–N coupling, it is still actively used in the field of organic synthesis.[17] The vinyl halides have some similar catalytic performance in the copper-catalyzed C–N coupling.[18] Inspired by Cesati III's research,[13b] we tried the CuI-catalyzed C–N coupling of bromobenzene and phenylalaninamide with *N,N′*-dimethylethylenediamine as ligand and $K_2CO_3$ as base. Fortunately, this reaction proceeded in toluene at 110 °C for 24 h and afforded only one new compound with 83% yield, which was verified to be L-phenylalanine anilide [i.e., (*S*)-2-amino-*N*,3-diphenylpropanamide] by spectral analysis and comparison with the literature data.[4d,5b]

Encouraged by our former study on ligand-free CuI-catalyzed cascade C–S/C–N coupling to synthesize phenanthiazines,[19] we tried ligand-free copper iodide as catalyst for this reaction. Interestingly, in the C–N cross-coupling of L-phenylalaninamide and bromobenzene, the simple, ligand-free copper catalytic system also afforded L-phenylalanine anilide with a marginally higher yield of 86%. That the two amino groups of the amino acid amides act as ligand to coordinate with copper could be the reason for this ligand-free catalysis. And thus additional ligands may influence this catalytic reaction and result in lower yields (see the Supporting Information). The ligand-free copper-catalyzed C–N coupling of the amide amino groups of phenylalaninamide is different from the classical copper-catalyzed C–N coupling of amides, which gave no yield when suitable 1,2-diamine ligand was not added.[20]

Since most of L-, D- and DL-form amino acid amides are commercially available and inexpensive, this protocol has the advantage of being direct (only one-step), atom-economic, ligand-free, practical and cost-effective.

Our research on the ligand-free copper-catalyzed selective C–N cross-coupling of amide amino groups of amino acid amides and aryl halides for the synthesis of chiral amino acid anilides will be described in detail below (Scheme 1).

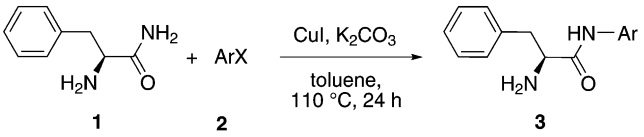
Firstly, we took L-phenylalaninamide and bromobenzene as the model substrates for the copper-catalyzed C–N cross-coupling to optimize the reaction conditions. After examining a series of copper sources, ligands, bases, solvents and temperatures (more detailed information may be found in the Supporting Information), finally we achieved the optimized reaction conditions: 5 mol% copper(I) iodide, $K_2CO_3$ (2 equivalents), L-phenylalaninamide (1.2 mmol), bromobenzene (1 mmol) in toluene (6 mL) at 110 °C for 24 h. Under the optimized reaction conditions, L-phenylalanine anilide **3a** was obtained exclusively.




**Scheme 1.** Ligand-free copper-catalyzed selective C–N cross-coupling of amide groups of amino acid amides and aryl halides.

With the optimized reaction conditions at hand, CuI-catalyzed C–N cross-couplings of various aryl halides and L-phenylalaninamide were examined. Since bromobenzene produced **3a** a high yield of up to 86% (Table 1, entry 1), more aryl bromides were evaluated: the C–N cross-coupling of *para*-bromotoluene and L-phenylalaninamide produced **3b** with approximately the same yield (Table 1, entry 2). Perhaps due to the steric hindrance, *ortho*-bromotoluene afforded **3d** with lower yield than *para*- and *meta*-bromotoluene (Table 1, entries 4 *vs.* 2 and 3). The electron property of the substituent group on the aryl bro-

**Table 1.** Copper-catalyzed C–N coupling of aryl halides and L-phenylalaninamide.[a]




| Entry | ArX | Product | Yield [%] |
|---|---|---|---|
| 1 | PhBr | **3a** | 86 |
| 2 | 4-Me-$C_6H_4Br$ | **3b** | 84 |
| 3 | 3-Me-$C_6H_4Br$ | **3c** | 76 |
| 4 | 2-Me-$C_6H_4Br$ | **3d** | 55 |
| 5 | 3-MeO-$C_6H_4Br$ | **3e** | 77 |
| 6 | 3-Br-$C_6H_4CN$ | **3f** | 81 |
| 7 | 4-$NO_2$-$C_6H_4Br$ | **3g** | 94 |
| 8 | 4-F-$C_6H_4Br$ | **3h** | 56 |
| 9 | PhI | **3a** | 96 |
| 10 | 4-Me-$C_6H_4I$ | **3b** | 93 |
| 11 | 3-I-$C_6H_4CN$ | **3f** | 93 |
| 12 | 4-F-$C_6H_4I$ | **3i** | 76 |
| 13 | PhCl | **3a** | 21 |
| 14 | 4-$NO_2$-$C_6H_4Cl$ | **3f** | 57 |
| 15 | 2-Br-pyridine | **3i** | 65 |
| 16 | 2-Br-thiophene | **3j** | 42 |
| 17 | β-Br-styrene | **3k** | 80 |

[a] *Reaction conditions:* L-amino acid amide (1.2 mmol), aryl halide (1.0 mmol), CuI (0.05 mmol), $K_2CO_3$ (2.0 mmol) and toluene (6 mL) for 24 h at 110 °C.

mide obviously influences the efficiency of this CuI-catalyzed *N*-arylation of the amide amino group of L-phenylalaninamide. As a substrate with an electron-donating group, coupling of 3-bromoanisole afforded **3e** with a good yield of 77% (Table 1, entry 5). As a substrate with an electron-withdrawing group, 3-bromobenzonitrile afforded the coupling product **3f** with a little better yield of 81% than 3-bromoanisole (Table 1, entry 6). 4-Bromonitrobenzene with a strong electron-withdrawing nitro group afforded **3g** with a much higher yield of up to 94% (Table 1, entry 7). Perhaps the fluoro group of 4-bromofluorobenzene took part in certain side reactions under the reaction conditions and produced by-products, so **3h** was obtained with a moderate yield (Table 1, entry 8).

Aryl iodides have much higher reactivity than the corresponding aryl bromides, i.e., all of the aryl iodides afforded much higher yields than the aryl bromides and chlorides. Furthermore, except for 1-fluoro-4-iodobenzene (Table 1, entry 12), other tested aryl iodides including iodobenzene, *para*-tolyl iodide and 3-iodobenzonitrile, all afforded the targeted chiral amino acid anilides with more than 90% yields (Table 1, entries 9–11).

However, aryl chlorides are poorer substrates for CuI-catalyzed *N*-arylation of L-phenylalaninamide. Chlorobenzene only gave a 21% yield (Table 1, entry 13); and the activated substrate *para*-chloronitrobenzene afforded a moderate yield (Table 1, entry 14).

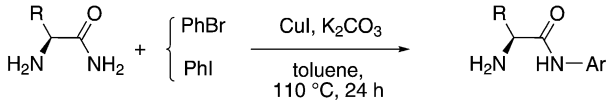
Heteroaryl bromides, 2-bromopyridine and 2-bromothiophene, also coupled with phenylalaninamide, but afforded the corresponding product **3i** and **3j** with moderate yields (Table 1, entries 15-16).

As a vinyl halide with less activity than vinyl iodides, β-bromostyrene was examined under our catalytic conditions and produced phenylalanine 2-phenylethenaminide **3k** with good yield (Table 1, entry 17).

Once aryl halides had been evaluated, the CuI-catalyzed C–N cross-couplings of various amino acid amides and bromobenzene or iodobenzene were investigated (Table 2). Coupling of L-phenylalaninamide with PhBr and PhI afforded (*S*)-*N*-(2-amino-3-phenylpropanoyl)benzamide **3a** with 86% and 96% yield, respectively (Table 2, entry 1). DL-Phenylalaninamide afforded nearly the same yield as the L-isomer (Table 2, entry 2).

In order to verify whether racemization occurred during the C–N cross-coupling, the enantiomeric excess of the product (*S*)-*N*-(2-amino-3-phenylpropanoyl)benzamide **3a** was analyzed by chiral HPLC on a Daicel Chiralcel OD-H column. The chiral HPLC results demonstrated the *ee* value of (*S*)-*N*-(2-amino-3-phenylpropanoyl)benzamide **3a** was as high as 99% (Table 2, entry 1), which means that no racemization occurred during the coupling. Phenylglycinamide, which is more apt to racemize, gave a partially racemized product at 110 °C. But at a lower temperature of 90 °C, 99% *ee* of phenylgly-

**Table 2.** Copper-catalyzed C–N coupling of aryl bromides or aryl iodides and amino acid amides.[a]




**1** **3**

| Entry | Amino acid amide | Amino acid anilide | Yield [%][b] (PhBr) | Yield [%][b] (PhI) |
|---|---|---|---|---|
| 1 | L-phenylalaninamide | **3a** | 86[c] | 96 |
| 2 | DL-phenylalaninamide | (±)-**3a** | 84 | N/A[d] |
| 3[e] | L-alaninamide hydrochloride | **3l** | 62 | 81 |
| 4[e] | L-valinamide hydrochloride | **3m** | 68 | 82 |
| 5 | L-leucinamide | **3n** | 73 | 86 |
| 6[e] | L-phenylglycinamide | **3o** | 72 | 90 (86)[f] |
| 7 | L-prolinamide | **3p** | 54 | 76 |
| 8 | L-ttryptophanamide | **3q** | 45 | N/A[d] |
| 9[e] | L-serinamide hydrochloride | **3r** | 0 | 0 |
| 10[e] | L-threoninamide hydrochloride | **3s** | 0 | 0 |
| 11[g] | L-phenylalaninamide | **3a** | 83 | 92 |

[a] *Reaction conditions:* L-amino acid amide (1.2 mmol), bromobenzene or iodobenzene (1.0 mmol), CuI (0.05 mmol), $K_2CO_3$ (2.0 mmol), and toluene (6 mL) for 24 h at 110 °C, unless otherwise noted.
[b] Isolated yields with bromobenzene and with iodobenzene as the substrates, respectively.
[c] Enantiomeric excess as checked by chiral HPLC on a Daicel Chiralcel OD-H is 99% *ee*.
[d] N/A means that no experiment was done, and so no yield is reported here.
[e] $K_2CO_3$ (3.0 mmol) was added.
[f] 99% *ee* and 86% yield were obtained at 90 °C for 24 h (Chiral HPLC trace is given in the Supporting Information).
[g] Ten times the amount of the reactants of entry 1 were used, and the reaction was performed under the same conditions.

cine anilide **3o** was obtained with 86% yield (Table 2, entry 6).

Prolinamide gave relatively lower yields than other amino acid amides, such as phenylalaninamide, alaninamide, valinamide, leucinamide, phenylglycinamide (Table 2, entry 7 *vs.* entries 1–6). Two possible reasons are that prolinamide has a secondary amino group and is apt to form a more stable copper complex.

Probably due to the effect of the indolyl group, tryptophanamide gave a moderate yield when it reacted with bromobenzene (Table 2, entry 8).

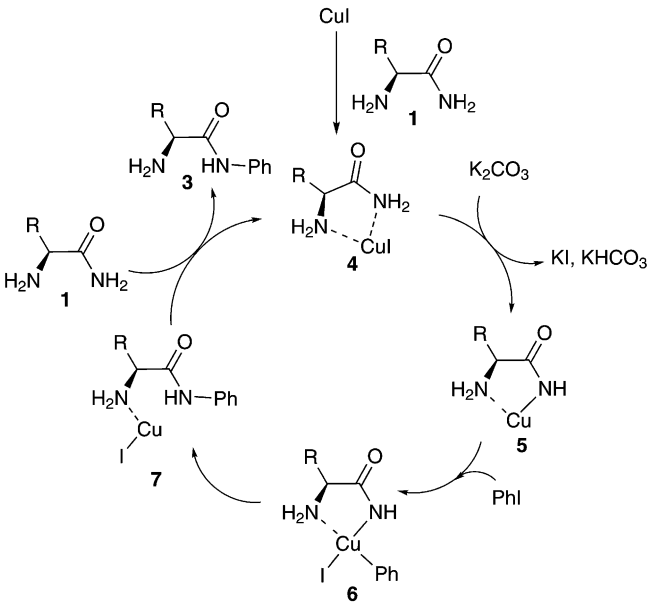
Neither bromobenzene nor iodobenzene coupled with serinamide or threoninamide (Table 2, entry 9 and 10). The reason probably is that the two amino acid amides have two amino groups and one hydroxy group in the right positions to act as tridentate ligands to undergo firm and stable coordination with copper, and the resulting copper complexes are too stable to react with bromobenzene or iodobenzene.

Iodobenzene and amino acid amides afforded the corresponding amino acid anilides (**3a** and **3l** to **3p**) with much better yields than bromobenzene (Table 2, entries 1 and 3 to 7).

Furthermore, the reaction could be scaled up to a gram scale without any problem (Table 2, entry 11).

As we known, copper can promote the *N*-arylation of both amines and amides.[17] But why does the copper catalyst selectively accomplish *N*-arylation of amide amino groups of amino acid amides? The reason may be attributed in the stronger electron-donating property of the aliphatic amino groups and the stronger acidity of the amide amino groups. On the one hand, the aliphatic amino groups have a stronger electron-donating property and thus stronger coordinating ability with copper than the amide amino groups. On the other hand, the amide amino groups possess stronger acidity than the aliphatic amino groups. Therefore the aliphatic amino group could not be deprotonated in the presence of free amide groups, and the amide amino groups were deprotonated and then reacted with aryl halides. Both of the reasons results in the sole formation of amino acid anilides.

A proposed mechanism is shown in Scheme 2. As a start, a copper(I) iodide molecule encounters a substrate amino acid amide molecule **1** under the reaction conditions, and then a copper(I) complex **4** of the amino acid amide is formed, analogues of which have reported.[21] The amide amino group of the complex **4** is facilely deprotonated by a $K_2CO_3$ molecule to produce a new copper(I) complex **5** with a σ bond between copper and the amide amino group.[21a] And at the same time KI and $KHCO_3$ are released. When the copper(I) complex **5** meets a PhI molecule, oxidative addition occurs and a tetracoordinated copper(III) complex **6** is obtained.[22] And then reductive elimination takes place to afford a new dicoordinated copper(I) complex **7**. Another amino acid amide molecule **1** drives the product **3** out of the catalytic cycle and forms the next copper(I) complex **4**, which begins a new catalytic cycle.




**Scheme 2.** A plausible mechanism for the CuI-catalyzed selective C–N cross-coupling of amino acid amides and iodobenzene.

In summary, we have discovered a direct, practical, cost-effective and atom-economic protocol for chemically selective copper-catalyzed selective C–N coupling of chiral amino acid amides and aryl halides, hetereoaryl halides and a vinyl bromide to synthesize chiral amino acid anilides, which are common core structures for a number of biologically important molecules, chiral catalysts, organocatalysts and organic synthetic intermediates. Furthermore, amino acid amides with 99% *ee* were obtained, which means that no racemization occurred during the C–N coupling. A mechanism of CuI-catalyzed selective C–N cross-coupling of the amide amino groups of chiral amino acid amides and iodobenzene was proposed.

## Experimental Section

### Typical Procedure for the CuI-Catalyzed Coupling Reaction of Amino Acid Amides with Aryl Halides

An oven-dried test tube with a stir bar was charged with L-phenylalaninamide (1.2 mmol), $K_2CO_3$ (2.0 mmol), and CuI (0.05 mmol). The test tube was sealed with a rubber stopper and evacuated and refilled with argon for three times. Under an argon atmosphere, iodobenzene (1.0 mmol) and toluene (6 mL) were added by a syringe (if the aryl halides are solid at room temperature, they were added at the same time with CuI and $K_2CO_3$). The tube was put into an oil

bath preheated at 110 °C and the mixture kept stirring at that temperature for 24 h. The reaction mixture was then cooled to room temperature, quenched with water, and extracted with ethyl acetate (20 mL) for three times. The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was condensed under reduced pressure. The residue was purified by silica gel column chromatography with a solution of petroleum ether and ethyl acetate (1/5 to 2/1) to afford L-phenylalanine anilide.

Procedures and analytical data for all compounds are given in the Supporting Information.

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