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# Ligand-free copper-catalyzed coupling of α-amino acids with N-Boc-2-iodoanilines for the synthesis of enantiopure 3-substituted dihydroquinoxalinones

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ABSTRACT

We report a room temperature and ligand-free copper-catalyzed coupling of α-amino acid with N-Boc-2-iodoanilines. The initially obtained N-arylated α-amino acids could be subsequently transformed into enantiomerically pure 3-aryl or 3-alkyl-substituted dihydroquinoxalinones via acid-mediated Boc-deprotection/condensation. It is of note that no racemization was observed during the two-step dihydroquinoxalinone synthesis, even when employing racemization-prone arylglycine amino acid starting materials.



Recently, we became interested in dihydroquinoxalinones as a scaffold with potential utility in early medicinal chemistry optimization of hits arising from High-Throughput Screening campaigns. The dihydroquinoxalinone motif is an important heterocycle found in several synthetic small molecules that display a variety of biological activities.[1] Two interesting approaches toward chiral 3-substituted-dihydroquinoxalin-2-ones include an enantioselective organocatalytic inverse electron demand cycloaddition between benzoquinone diimides and ketene enolates,[2] and a dynamic kinetic resolution via reaction of 1,2-dianilides with α-halo esters.[3] Although the former occurs with high enantioselectivity, it requires a 2-step synthesis of bis-benzoylated *o*-benzoquinone diimide starting materials; whereas the latter suffers from less than ideal enantioselectivities (ee's ⩽90%), is auxiliary-based, and is limited in scope by virtue of the necessity to engage sufficiently reactive α-halo esters. The more recent organocatalytic transfer reduction or Ir(I)-catalyzed hydrogenation of quinoxalinones proceeds with excellent enantioselectivity, but appears to be limited to primarily 3-aryl-substituted substrates.[4,5] All of the above approaches ultimately suffer from the same symmetry-related limitation in substrate scope, in as much that they all track back to 1,2-dianilide starting materials, which will yield regioisomeric mixtures of dihydroquinoxalinone products,[2,3] or quinoxalinone starting materials if the subtly dissimilar anilide nitrogens in unsymmetrical 1,2-dianilides cannot be differentiated.[4,5]

A more traditional approach that does not suffer from the above symmetry-drawback is the $S_NAr$ reaction of α-amino acids or e sters with *o*-fluoronitrobenzenes followed by reductive cyclization,[1a,b,f–h,6] but (partial) racemization is often observed especially with arylglycine substrates.[6b,c] The room temperature Cu(I)-catalyzed N-arylation of amino acids with *o*-iodonitrobenzene followed by reductive cyclization appears to be a milder alternative to 3-substituted-dihydroquinoxalin-2-ones, although racemization issues were not discussed, nor were epimerization-prone arylglycine substrates included.[7,8] Finally, Tanimori et al. described a related Cu(I)-catalyzed N-arylation of amino acids with *o*-bromoaniline followed by in situ cyclodehydration.[9] Given the vast range of readily available natural and unnatural α-amino acids, often in both antipodal configurations, we were attracted to this one-pot assembly of 3-substituted-dihydroquinoxalinones despite the necessity for 2 equiv of amino acid.[10] Of note was the configurational stability of the products to the rather strongly basic conditions ($K_3PO_4$ or DBU) and high reaction temperature (120 °C), with the caveat that configurationally labile arylglycines were not explored.[9b] Thus, when we observed that phenylglycine decomposed and no desired product was obtained when applying Tanimori's conditions,[9b] which we successfully reproduced for the corresponding reaction with serine (Eq. (1)), we decided to formulate a solution that would expand the scope to include arylglycines.

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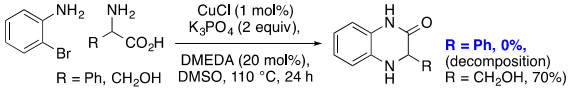


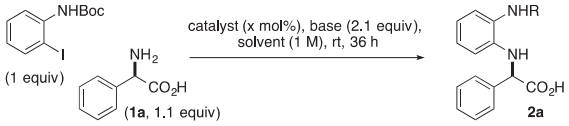

(1)

Herein, we disclose a room temperature and ligand-free copper-catalyzed coupling of α-amino acids with N-Boc-2-iodoanilines to yield intermediate *N*-aryl α-amino acids, which were further transformed into chiral quinoxalinones upon acid-treatment. Moreover, we found that *N*-aryl α-amino acids derived from arylglycines converted into 2-arylbenzimidazoles via oxidative decarboxylation when heated in air.

We initiated our studies by examining the copper-catalyzed coupling between 2-haloanilines and phenylglycine (Table 1). As noted above in (Eq. (1)), phenylglycine decomposed in attempts to arylate it with 2-bromoaniline under the reaction conditions reported by Tanimori.[9b] Unfortunately, engaging the more reactive 2-iodoaniline or N-Boc-protected-2-bromo or iodoaniline under the same reaction conditions equally lead to phenylglycine decomposition, and no desired coupling product was observed (entries 1–3). We suspected that oxidative decarboxylation of 2-amino-2-phenylacetic acid (phenylglycine) was the culprit at these higher temperatures,[11] and therefore decided to identify conditions that would affect cross-coupling at room temperature. Based on Ma's original observation that amino acids can accelerate CuI-catalyzed cross coupling of amines, including amino acids,[8a] we next explored room temperature ligandless conditions with 10 mol % CuI as the catalyst and $Cs_2CO_3$ as the base.[12] As shown in entries 4 and 5, unprotected haloanilines (I, Br) were unreactive as was the N-Boc-protected bromoaniline (entry 6). Gratifyingly, the corresponding N-Boc-2-iodoaniline smoothly reacted with phenylglycine at room temperature to yield the N-arylated product **2a** in 84% isolated yield (entry 7).

In Table 2, we document a survey of reaction conditions (catalyst, base, solvent) for the room temperature, ligand-free, copper-catalyzed cross coupling of phenylglycine (**1a**) with N-Boc-2-iodoaniline to N-arylated phenylglycine **2a**. In addition to CuI, other copper catalysts such as CuCl, CuBr, and $Cu(OTf)_2$ effected the desired transformation, albeit with ~10% lower yields (entries 1–3 vs entry 4). Among the different bases, $Cs_2CO_3$ provided the best results (entries 4, 84%), whereas potassium phosphate (entry 5, 58%), potassium carbonate (entry 6, 8%), and sodium bicarbonate (entry 7, 0%) dramatically impacted conversion. A cursory solvent screen revealed DMSO to be superior to DMF, DMA, and NPM (entry 4 vs entries 8–10). As shown in entry 11, the amount of CuI catalyst could be lowered to 5 mol % without impacting the overall isolated yield. However, further reducing the catalyst load to 2 mol % reduced the yield by half (entry 12).

**Table 2**
Optimization of reaction conditions[a]

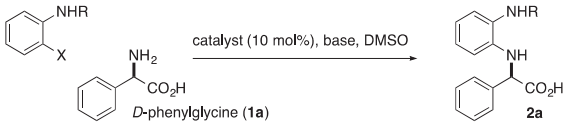



| Entry | Catalyst | mol % | Base | Solvent | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | CuCl | 10 | $Cs_2CO_3$ | DMSO | 75 |
| 2 | CuBr | 10 | $Cs_2CO_3$ | DMSO | 72 |
| 3 | $Cu(OTf)_2$ | 10 | $Cs_2CO_3$ | DMSO | 70 |
| 4 | CuI | 10 | $Cs_2CO_3$ | DMSO | 84 |
| 5 | CuI | 10 | $K_3PO_4$ | DMSO | 58 |
| 6 | CuI | 10 | $K_2CO_3$ | DMSO | 8 |
| 7 | CuI | 10 | $NaHCO_3$ | DMSO | 0 |
| 8 | CuI | 10 | $Cs_2CO_3$ | DMA | 69 |
| 9 | CuI | 10 | $Cs_2CO_3$ | DMF | 71 |
| 10 | CuI | 10 | $Cs_2CO_3$ | NMP | 67 |
| 11 | CuI | 5 | $Cs_2CO_3$ | DMSO | 83 |
| 12 | CuI | 2 | $Cs_2CO_3$ | DMSO | 44 |

[a] Reaction conditions: N-Boc-2-iodoaniline (0.5 mmol), phenylglycine (0.55 mmol), catalyst (0–10 mol %), base (1.05 mmol), solvent (0.5 mL), rt, 36 h.
[b] Isolated yields.

Next, we explored the scope of the Cu(I)-catalyzed N-arylation of various α-amino acids with a selection of N-Boc-2-idoanilines using the above optimized reaction conditions (5 mol % CuI catalyst, 1 equiv ArI, 1.1 equiv amino acid, 2.1 equiv $Cs_2CO_3$, DMSO, rt, 36–72 h). As shown in Figure 1, valine, phenylalanine, and tryptophan-derived coupling products **2h–j** were obtained in good to excellent yields (74–90%). It is noteworthy that tryptophan did not require indole nitrogen protection and no competing N-indole arylation products were detected. Even more excitingly, a range of arylglycine-derived coupling products were obtained in acceptable

**Table 1**
Identification of reaction conditions for the Cu(I)-catalyzed N-arylation of phenylglycine (**1a**)[a]




| Entry | ArX | Catalyst (mol %) | Base | Temp (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | R = H<br>X = I | CuCl (1) | $K_3PO_4$ | 110 | 24 | 0[c] |
| 2 | R = Boc<br>X = Br | CuCl (1) | $K_3PO_4$ | 110 | 24 | 0[c] |
| 3 | R = Boc<br>X = I | CuCl (1) | $K_3PO_4$ | 110 | 24 | 0[c] |
| 4 | R = H<br>X = Br | CuI (10) | $Cs_2CO_3$ | rt | 48 | 0[d] |
| 5 | R = H<br>X = I | CuI (10) | $Cs_2CO_3$ | rt | 48 | 0[d] |
| 6 | R = Boc<br>X = Br | CuI (10) | $Cs_2CO_3$ | rt | 36 | 0[d] |
| 7 | R = Boc<br>X = I | CuI (10) | $Cs_2CO_3$ | rt | 36 | 84 |

[a] Reaction conditions: for entries 1–3, ArX (0.5 mmol), phenylglycine (1 mmol), CuCl (1 mol %), DMEDA (20 mol %), $K_2PO_4$ (1 mmol), DMSO (1.8 mL); for entries 4–7, ArX (0.5 mmol), phenylglycine (0.55 mmol), CuI (10 mol %), $Cs_2CO_3$ (1.05 mmol), DMSO (0.5 mL).
[b] Isolated yields.
[c] Decomposition of phenylglycine (**1a**).
[d] No reaction.