Arylglycine-derivative synthesis via oxidative sp³ C–H functionalization of α-amino esters

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Abstract
An efficient method for the synthesis of arylglycine derivatives is described. The oxidative coupling reactions of naphthols and phenols with α-amino esters proceeded smoothly in the presence of meta-chloroperoxybenzoic acid as an oxidant under ambient conditions, to produce arylglycine derivatives in satisfactory yields.

Findings
Arylglycine derivatives represent important synthetic intermediates or building blocks for drug development and natural-product synthesis [1,2]. The arylglycine moiety also occurs in several bioactive natural products [3]. Consequently, the development of convenient and efficient methods for the preparation of arylglycine derivatives has attracted considerable attention. Over the past years, many methods have been developed for the preparation of arylglycine derivatives [3]. Among these, the addition reaction of a carbon nucleophile to imines or iminium ions through Mannich-type reaction appears more useful (Scheme 1, reactions 1–3). However, these reactions need expensive aryloboronic acids (Petasis reaction) [4-9] and suitable leaving groups [10-12] as well as a metal catalyst (Polonovsky reaction; this route requires the preparation of amine N-oxide in advance) [13,14].

We have recently reported the copper-catalyzed oxidative coupling reaction of alkynes with tertiary amine N-oxides [15]. This new strategy for the direct functionalization of sp³ C–H bonds adjacent to a nitrogen atom, via tertiary amine N-oxide intermediates, was successfully applied to the coupling reaction of ethyl 2-(disubstituted amino)acetates with indoles to achieve indolylglycine derivatives (Scheme 2, reaction 1) [16]. In the course of our continuous research on the direct functionalization of sp³ C–H bonds, we found that this new strategy could also be applied to the coupling reaction of naphthols and phenols with ethyl 2-(disubstituted amino)acetates. The results are reported in the current work (Scheme 2, reaction 2).

In our initial studies, the reaction of 2-naphthol (1a) with ethyl 2-morpholinoacetate (2a) was chosen as a model for opti-
Scheme 1: Synthesis of arylglycine derivatives.

Scheme 2: Oxidative sp^3 C–H functionalization of α-amino esters.

mCPBA oxidized 2a to amine N-oxide 4 before being transformed into 3-chlorobenzoic acid. The interaction of 4 with 3-chlorobenzoic acid led to the generation of the iminium ion 5 and 3-chlorobenzoate anion. The Mannich-type reaction of 5 with 2-naphthol may have occurred to generate the coupling product 3a. The generated 3-chlorobenzoate anion acted as a proton acceptor.

The plausible mechanism for the coupling reaction of naphthols and phenols with ethyl 2-aminoacetate derivatives is shown in Scheme 3 [16-19]. mCPBA oxidized 2a to amine N-oxide 4 before being transformed into 3-chlorobenzoic acid. The interaction of 4 with 3-chlorobenzoic acid led to the generation of the iminium ion 5 and 3-chlorobenzoate anion. The Mannich-type reaction of 5 with 2-naphthol may have occurred to generate the coupling product 3a. The generated 3-chlorobenzoate anion acted as a proton acceptor.
Table 1: Optimization of reaction conditions.a

| Entry | 2a (equiv) | mCPBA (equiv) | Time (h) | Solvent | Yield of 3a (%)b |
|-------|------------|---------------|----------|---------|-----------------|
| 1     | 1.0        | 1.0           | 40       | CH3CN   | 63              |
| 2     | 1.2        | 1.2           | 40       | CH3CN   | 77              |
| 3     | 1.5        | 1.5           | 40       | CH3CN   | 77              |
| 4c    | 1.2        | 1.2           | 40       | CH3CN   | 75              |
| 5     | 1.2        | 1.2           | 24       | CH2Cl2  | 79              |
| 6     | 1.2        | 1.2           | 40       | THF     | 65              |
| 7     | 1.2        | 1.2           | 48       | dioxane | 16              |
| 8     | 1.2        | 1.2           | 48       | CH3CH2OH| 14              |
| 9     | 1.2        | 1.2           | 48       | toluene | 70              |
| 10    | 1.2        | 1.2           | 48       | DMF     | trace           |

aReactions conditions: 2-naphthol (1a, 72.1 mg, 0.5 mmol), ethyl 2-morpholinoacetate (2a, 1.0 equiv to 1.5 equiv), and mCPBA (1.0 equiv to 1.5 equiv) in solvent (3.0 mL) under air at 25 °C. bIsolated yield. c10 mol % Cu(OTf)2 was used as a catalyst.

Table 2: Oxidative coupling reaction of naphthols and phenols with α-amino esters.a

| Entry | Phenol 1 | Amine 2 | Time (h) | Product 3 | Yield (%)b |
|-------|----------|---------|----------|-----------|------------|
| 1     | 1a       | 2a      | 24       | 3a        | 79         |
| 2     | 1a       | 2b      | 24       | 3b        | 64         |
| 3     | 1a       | 2c      | 36       | 3c        | 64         |
Table 2: Oxidative coupling reaction of naphthols and phenols with α-amino esters.\(^a\) (continued)

|   | Reaction conditions: naphthols or phenols (1, 0.5 mmol), α-amino esters (2, 0.6 mmol, 1.2 equiv), and mCPBA (121.8 mg, 0.6 mmol, 85% purity) in CH\(_2\)Cl\(_2\) (3.0 mL) under air at 25 °C. \(^a\)Isolated yield. |   |
|---|---|---|
| 4 | 1b | 20 | 79 |
| 5 | 1c | 20 | 75 |
| 6 | 1d | 18 | 66 |
| 7 | 1e | 48 | 30 |
| 8 | 1f | 36 | 30 |
| 9 | 1g | 24 | 35 |
| 10 | 1h | 16 | 55 |
| 11 | 1i | 48 | 0 |

\(^a\)Isolated yield.
In conclusion, a new strategy for the functionalization of sp³ C–H bonds of amino esters was successfully applied to the coupling reaction of ethyl 2-(disubstituted amino)acetates with naphthols and phenols. The proposed coupling reaction proceeded smoothly in the presence of mCPBA as an oxidant under ambient conditions to provide arylglycine derivatives in satisfactory yields.

Supporting Information
Supporting Information File 1
General methods, characterization data and NMR spectra of all synthesized compounds.

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