Oxidative cross-coupling reaction by scandium catalysis for synthesis of \(\alpha\)-alkyl \(\alpha\)-amino acid ester derivatives†

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In the past decade, the oxidative coupling reaction has become a new method to afford \(\text{C-C}\) bonds from \(\text{C-H}\) bonds due to its being atom economical and environmentally friendly.¹ Meanwhile, \(\alpha\)-amino acids play an important role in natural products and are the key structural motifs of numerous natural products.² Therefore, the oxidative coupling reaction of glycine derivatives has gained significant attention for the synthesis of a series of \(\alpha\)-substituted \(\alpha\)-amino acid derivatives.³ For example, Li’s group designed the first method for an oxidative dehydrogenative coupling reaction to synthesize \(\alpha\)-amino glycine derivatives from \(N\)-glycine derivatives by direct \(\text{C-C}\) bond formation.⁴ Subsequently, Huang’s group disclosed a cross-dehydrogenative coupling reaction with \(N\)-arylglycine esters to synthesize \(\alpha\)-amino glycine derivatives under the cooperative catalysis of copper salt.⁵ Recently, the oxidative coupling of \(N\)-glycine derivatives has been well developed under stoichiometric amounts of chemical oxidants such as DTBP, DDQ, TBHP and 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (T°BF₄).⁶ Furthermore, transition metal-catalyzed synthesis of chiral \(\alpha\)-amino acid derivatives by direct \(\text{C-H}\) oxidative cross-coupling has been reported in the past few years.⁷ For example, Wang’s group developed a significant method of chiral Lewis acid controlled enantioselective alkylation of \(\alpha\)-Csp²–H bonds to synthesize chiral alky \(\alpha\)-amino acid derivatives.⁸ Another effective pathway to synthesize \(\alpha\)-amino acids has been reported by palladium-catalyzed \(\text{C-H}\) functionalization.⁹ Recently, Yang’s group found a novel pathway for the synthesis of chiral \(\alpha\)-amino acid derivatives from aryl boronic acids by \(\text{Pd(II)}\)-catalysis with direct \(\text{C-H}\) oxidation (1, Scheme 1),¹⁰ but only \(\alpha\)-aryl \(\alpha\)-amino acid ester derivatives were obtained. However, for the synthesis of benzylo \(\alpha\)-amino acid derivatives by the oxidative cross-coupling reaction of glycine derivatives, very few examples have been reported to date.¹¹ Based on this considerable progress, in this paper, we describe a novel strategy for the cross-coupling reaction between \(N\)-arylglycine esters and boronic acid esters for the synthesis of \(\alpha\)-alkyl \(\alpha\)-amino acid esters in the presence of \(\text{Sc(III)}\)-catalyst (2, Scheme 1).

In an initial study, we chose \(N\)-arylglycine esters 1a as the model substrates with benzylboronic acid esters¹² 2a as alkylatation reagents, \(\text{PPh₃}\) as the ligand, and BQ as the oxidant in the presence of 10 mol% \(\text{Cu(OTf)}₂\) in \(\text{DCE}\) at 80 °C. We were pleased to find that the desired product \(\alpha\)-alkyl \(\alpha\)-amino acid ester 3a was observed in 32% yield (Table 1, entry 1). Encouraged by this result, screening several oxidants (Table 1, entries 2–9) showed that \(\text{Ag₂CO₃}\) was the best choice, and the yield of 3a improved to 70% (Table 1, entry 6). When the oxidant was increased to 2 equiv., the yield of 3a reached 78% (Table 1, entry 11). Subsequently, various solvents were examined and \(\text{DCE}\) was still found to be the best choice (Table 1, entries 12–16). Then, a variety of different Lewis acids were investigated, and \(\text{Sc(OTf)}₃\) proved to be the best with 85% yield for coupling product 3aa (Table 1, entries 17–21). Furthermore, the control experiment showed that only 15% yield of the desired product was obtained in the absence of \(\text{Sc(OTf)}₃\) (Table 1, entries 22–23).

**Scheme 1**  Reaction of glycine derivatives with metal boron reagents.

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a few substrates containing substituents with electron-donating bromophenyl glycine ethyl ester as the substrate, and prepared a group from the available starting materials. The corresponding product in moderate yield (Table 2, entries 18–20) was obtained only in 22% yield; no product in 68% yield (Table 2, entries 15–16). When the aniline fragment changed to N-para formylation, we selected the appropriate oxidant (1.5 equiv.) and Ag2CO3 (2.0 equiv.) were stirred in DCE (2.5 mL) at 80 °C under Ar for 20 h. Yield of the isolated products.

Under the optimized reaction conditions (Table 1, entry 21), the reaction scope was examined as shown in Table 2. We first surveyed various N-para-bromophenyl protected glycine esters. It was found that various alkyl esters including methyl 1b and tert-butyl 1c were well tolerated in the oxidative C–H functionalization with N-arylglycine esters 1a, affording α-alkyl α-amino acid esters 3a–3c in 78–85% yields (Table 2, entries 3a–3c). Meanwhile, different substituents on the aniline fragment, which bear electron-withdrawing or electron-donating groups, afforded the corresponding desired products in moderate to excellent yields (Table 2, entries 3d–3g). However, the electronic effect in this transformation was very notable, for example, when the aniline fragment changed to N-para-methoxysyphenyl, the corresponding product was obtained only in 22% yield; no substituent on the aniline fragment afforded the desired product in moderate yield (Table 2, entries 3g–3h). In order to further expand the substrate scope, we selected the N-para-bromophenyl glycine ethyl ester as the substrate, and prepared a few substrates containing substituents with electron-donating or electron-withdrawing effects on other positions of the benzyl group from the available starting materials. The corresponding α-amino acid ester products were obtained in good to excellent yields (Table 2, entries 3i–3p). Furthermore, the naphthylboronic acid ester could also undergo transformation and afford the product in 68% yield (Table 2, 3l).

Moreover, to extend the scope of this catalytic system, we conducted direct functionalization of the α-peptido C–H bonds under the optimized reaction conditions. We were pleased to find that the corresponding α-alkylation product 4aa was obtained in good yield (Scheme 2). We believe that the yield of the product will increase accordingly, after appropriate optimization of the catalytic system. This work is currently under way in our laboratory.

To investigate the mechanism of this transformation, experiments were carried out. The desired product was not observed when 1.0 equivalent of the radical-trapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used under the standardized reaction conditions. At the same time, we found that when 2,6-di-tert-butyl-4-methylphenol (BHT), a radical scavenger, was introduced into the reaction system, the yield of product 3a decreased dramatically from 85% to 8% (Scheme 3). To our delight, BHT trapped the key intermediate, which was detected by GC-MS (see ESI†). This result suggests that the reaction may proceed via a radical mechanism (Scheme 4). First, benzylicboronic acid ester 2a forms the intermediate benzyl radical 5 under the oxidation of Ag2CO3; at the same time, radical 6 is generated by abstracting an α hydrogen atom from N-arylglycine ester 1a under oxidant. Then the product 3aa is obtained through the radical addition reaction (Scheme 4, path 3aa).

![Scheme 2](image-url) Extending the scope of the catalytic system.
A). Then, single-electron transfer (SET) occurs from 6 to cation 7, which can tautomerize to the iminium ion. At the same time, Sc(OTf)₃ with the ligand PPh₃ reacts as a Lewis acid with 7 to form the active species intermediate 1A. Then intermediate 1B is produced though Petasis-type addition of benzylic boronic acid 2a to the iminium intermediate.²⁻¹⁰ Finally, product 3aa is obtained upon dissociation in the presence of HOTf, and the active scandium catalyst is regenerated and enters the next catalytic cycle synchronously (Scheme 4, path B).

In conclusion, we have developed a mild and economical Sc(OTf)₃-catalyzed oxidative cross-coupling reaction for the synthesis of a series of α-alkyl α-amino acid ester derivatives. Further applications of this approach to other substrates and enantioselective reactions are being investigated in our laboratory.

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Notes and references


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