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Oxidative cross-coupling reaction by scandium catalysis for synthesis of α -alkyl α -amino acid ester derivatives†

Xiao-Hong Wei,* Lian-Biao Zhao* and Han-Cheng Zhou

A novel oxidative cross-coupling reaction between N-arylglycine esters and alkyl boronic acid esters for synthesis of α -alkyl α -amino acid esters in the presence of scandium catalysis using silver salt as an oxidant has been developed. The mild reaction has an excellent functional group tolerance and gives the desired α -alkyl α -amino acid esters in a moderate to excellent yield.

In the past decade, the oxidative coupling reaction has become a new method to afford C-C bonds from C-H bonds due to it being atom economical and environmentally friendly.1 Meanwhile, α-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 α -substituted α -amino acid derivatives.³ For example, Li's group designed the first method for an oxidative dehydrogenative coupling reaction to synthesize α-amino glycine derivatives from N-glycine derivatives by direct C-C bond formation.34 Subsequently, Huang's group disclosed a crossdehydrogenative coupling reaction with N-arylglycine esters to synthesize α-amino glycine derivatives under the cooperative catalysis of copper salt.3b Recently, the oxidative coupling of Nglycine 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⁻). Furthermore, transition metal-catalyzed synthesis of chiral α-amino acid derivatives by direct C-H oxidative cross-coupling has been reported in the past few years.⁵ For example, Wang's group developed a significant method of chiral Lewis acid controlled enantioselective alkylation of α-C_{sp3}-H bonds to synthesize chiral alkyl α-amino acid derivatives.⁶ Another effective pathway to synthesize chiral αamino acids has been reported by palladium-catalyzed C-H functionalization.7 Recently, Yang's group found a novel pathway for the synthesis of chiral α-amino acid derivatives from aryl boronic acids by Pd(II)-catalysis with direct C-H oxidation (1, Scheme 1),5g but only α-aryl α-amino acid ester

derivatives were obtained. However, for the synthesis of benzyl α -amino acid derivatives by the oxidative cross-coupling reaction of glycine derivatives, very few examples have been reported to date. 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 α -alkyl α -amino acid esters in the presence of Sc(III)-catalyst (2, Scheme 1).

In an initial study, we chose N-arylglycine esters 1a as the model substrates with benzylboronic acid esters9 2a as alkylation reagents, PPh3 as the ligand, and BQ as the oxidant in the presence of 10 mol% Cu(OTf)₂ in DCE at 80 °C. We were pleased to find that the desired product α-alkyl α-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 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 DCE was still found to be the best choice (Table 1, entries 12-16). Then, a variety of different Lewis acids were investigated, and 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 Sc(OTf)3 (Table 1, entries 22-23).

Scheme 1 Reaction of glycine derivatives with metal boron reagents.

Key Laboratory for Utility of Environment-Friendly Composite Materials and Biomass in University of Gansu Province, College of Chemical Engineering, Northwest University for Nationalities, Lanzhou 730030, P. R. China. E-mail: weixh12@lzu.edu.cn; 1146868630@qq.com

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Yang's group $R_{1} \stackrel{H}{ \cup \cup} CO_{2}R_{2} + Ar - B(OH)_{2} \stackrel{Pd(II)/Ligand}{ \cup} R_{1} \stackrel{H}{ \cup} A_{r} CO_{2}R_{2}$ $R_{1} \stackrel{H}{ \cup} CO_{2}R_{2} + Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} A_{r} CO_{2}R_{2}$ $R_{1} \stackrel{H}{ \cup} CO_{2}R_{2} + Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Alkyl - BO \stackrel{O}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Sc(IIII) \rightarrow R_{1} \stackrel{H}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Sc(IIII) \rightarrow R_{1} \stackrel{H}{ \cup} Sc(III) \rightarrow R_{1} \stackrel{H}{ \cup} Sc(IIII) \rightarrow R_{1} \stackrel{H}{ \cup} Sc(III) \rightarrow$

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst	Ligand	Oxidant	Solvent	Yield ^b
1	Cu(OTf) ₂	PPh_3	BQ	DCE	32%
2	$Cu(OTf)_2$	PPh_3	DDQ	DCE	ND
3	$Cu(OTf)_2$	PPh_3	TBHP	DCE	Trace
4	$Cu(OTf)_2$	PPh_3	$PhI(OAc)_2$	DCE	Trace
5	$Cu(OTf)_2$	PPh_3	DCP	DCE	43%
6	$Cu(OTf)_2$	PPh_3	Ag_2CO_3	DCE	70%
7	Cu(OTf) ₂	PPh_3	AgOAc	DCE	68%
8	$Cu(OTf)_2$	PPh_3	Ag_2O	DCE	53%
9	$Cu(OTf)_2$	PPh_3	$AgNO_3$	DCE	ND
10^{c}	$Cu(OTf)_2$	PPh_3	Ag_2CO_3	DCE	72%
11^d	$Cu(OTf)_2$	PPh_3	Ag_2CO_3	DCE	78%
12^d	$Cu(OTf)_2$	PPh_3	Ag_2CO_3	CH_3CN	11%
13^d	$Cu(OTf)_2$	PPh_3	Ag_2CO_3	NMP	ND
14^d	$Cu(OTf)_2$	PPh_3	Ag_2CO_3	TOL	13%
15^d	$Cu(OTf)_2$	PPh_3	Ag_2CO_3	DMF	15%
16^d	$Cu(OTf)_2$	PPh_3	Ag_2CO_3	Dioxane	23%
17^{d}	$Zn(OTf)_2$	PPh_3	Ag_2CO_3	DCE	81%
18^d	$Ni(OTf)_2$	PPh_3	Ag_2CO_3	DCE	33%
19^d	$Al(OTf)_2$	PPh_3	Ag_2CO_3	DCE	79%
20^d	Fe(OTf) ₂	PPh_3	Ag_2CO_3	DCE	56%
21^d	Sc(OTf) ₃	PPh_3	Ag_2CO_3	DCE	85%
22^d			Ag_2CO_3	DCE	10%
23	$Sc(OTf)_3$		-	DCE	15%

^a Reaction conditions: **1a** (0.3 mmol), **2a** (1.3 equiv.), catalyst (10 mol%), ligand (10 mol%) and oxidant (1.1 equiv.) were stirred in solvent (1 mL) at 80 $^{\circ}$ C under Ar for 20 h. ^b Yield of the isolated product. ^c Oxidant (1.5 equiv.). ^d Oxidant (2.0 equiv.).

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-methoxyphenyl, 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-parabromophenyl 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 vields (Table 2, entries 3i-3p). Furthermore, the naphthylboronic acid ester could also undergo transformation and afford the product in 68% yield (Table 2, 31).

Table 2 Scope of synthesis of various α -amino acid esters^{ab}

Moreover, to extend the scope of this catalytic system, we carried out 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 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, benzylboronic 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

Scheme 2 Extending the scope of the catalytic system.

^a Reaction conditions: **1a** (0.3 mmol), **2a** (1.3 equiv.), Sc(OTf)₃ (10 mol%), PPh₃ (10 mol%) and Ag₂CO₃ (2.0 equiv.) were stirred in DCE (2.5 mL) at 80 °C under Ar for 20 h. ^b Yield of the isolated products.

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Scheme 3 Radical-trapping experiment.

Scheme 4 Proposed mechanism.

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. 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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