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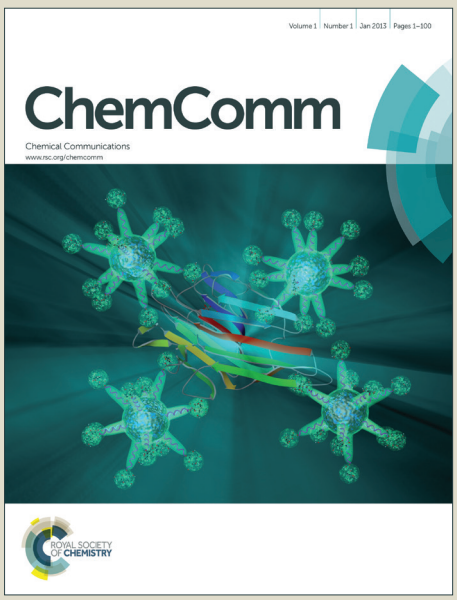

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Enantioselective Synthesis of Arylglycine Derivatives by Direct C–H Oxidative Cross-coupling

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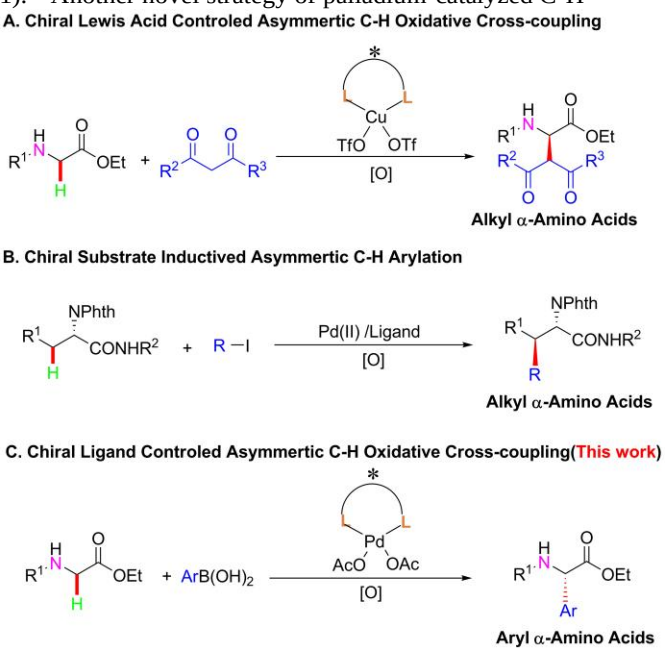
A new method for the synthesis of chiral α–amino acids derivatives by enantioselective C-H arylation of *N*-aryl glycine esters with aryl boric acids in the presence of a chiral Pd(II)-catalyst has been developed. This work successfully integrates the direct C-H oxidation with asymmetric arylation and exhibits the excellent enantioselectivity.

Chiral α–amino acids are useful compounds of great interest and frequently constitute the cores of peptides, proteins, and pharmaceutical agents.[1] These amino acids have also been used in organic chemistry to synthesize natural products or as chiral auxiliaries, catalysts, or catalyst ligands.[2] Therefore, the discovery of general methodology that can produce chiral α–amino acid derivatives in high yield and with useful levels of enantioselectivity is of considerable importance.[3] Up to present, relatively straightforward catalytic asymmetric approaches to chiral α–amino acid derivatives mainly include the asymmetric Strecker reaction,[4] direct amination reaction involving metal-carbenes,[5] and transition metal-catalyzed asymmetric hydrogenation of α–enamides[6] or imino esters.[7] Furthermore, transition metal-mediated asymmetric addition of various nucleophiles to α–imino esters[8] also provides for the development of concise and attractive routes to synthesize optically active α–amino acid derivatives. Recently, the use of asymmetric alkylation of benzophenone Schiff base glycine esters with phase-transfer catalysts (PTCs)[9] has established direct approaches to such compounds and has shown impressive progress. Despite tremendous significant achievements in this field, the development of more efficient and practical methods for convenient construction of various chiral α–amino acids remains a difficult but potentially rewarding challenge given the great demand for these compounds.

Over the past decades, various high efficiency and versatile protocols for the C-H activation have been demonstrated,[10] especially the building of C-C and C-heteroatom bonds directly from two simple C-H bonds or C-H and carbon nucleophiles have emerged as a highly valuable strategy for C-C bond formations and been studied extensively because of their great ecological and high atom economy.[11] However desirable, realization of stereo-, and enantioselective C_{sp3}–C bond formations by direct C-H oxidative remains a challenging task.[12] For the synthesis of chiral α–amino acid derivatives, very few examples have been reported to date. Recently, Wang and coworkers disclose a significant method of chiral Lewis acid controlled asymmetric C-H oxidative cross-coupling to synthesize chiral alkyl α–amino acid derivatives (**A**, Scheme 1).[13] Another novel strategy of palladium-catalyzed C-H



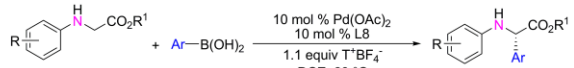
Scheme 1. Various Strategies for the Synthesis of Chiral α–Amino acid Derivatives.

functionalization of chiral α–amino acids also provides an effective pathway (**B**, Scheme 1).[14] However, these two strategies are subject to substrates and only have been applied to synthesize chiral alkyl α–amino acid derivatives. The example of synthesize the chiral aryl α–amino acid derivatives by direct C-H arylation has not been reported. In this paper, we describe a novel strategy and approach: a highly efficient route to chiral arylglycine derivatives via the enantioselective cross-coupling of aryl boric acids to *N*-aryl glycine esters in the presence of a chiral Pd(II)-catalyst that successfully integrates direct C-H oxidation with asymmetric arylation (**C**, Scheme-1).

In an initial study, we chose *para*-methoxyphenyl-(PMP)-protected glycine ester **1a** and *para*-methyphenyl boric acid as model substrates to identify suitable reaction conditions (Table 1, see Supporting Information). We first selected achiral 2,2-bipyridine as ligand and 10 mol % $Pd(OAc)_2$ as catalyst to screen different oxidants; to our delight the desired product of racemic **2a** was obtained in 32% yield by using the 2,2,6,6-tetramethylpiperidine-1-oxoammonium *tetra*-fluoroborate ($T^+BF_4^-$) as an oxidant at 60 °C. Subsequently, diverse solvents screening showed that the 1,2-dichlorethane (DCE) is the best choice; the yield of **2a** improved to 70% yield (see supporting information for details). Based on these results, the enantioselective C-H oxidative cross-coupling between *para*-methoxyphenyl-(PMP)-protected glycine ester **1a** with *para*-methyphenyl boric acid was carried out in the presence of 10 mol% $Pd(OAc)_2$ with various chiral ligands in DCE at 60 °C (table 1, entries 1-9). As expected, the best result was observed by employing **L8** as a ligand: chiral α–amino acids ester of **2a** afforded in 69% yield and 90% ee value (table 1, entry 8). After, we fixed the chiral ligand as **L8** and evaluated some solvents again. Results indicated that the DCE is still the best choice (Table 1, entries 9-15). We also examined other palladium catalysts such as $PdCl_2$, $Pd(TFA)_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(CH_3CN)_2(OTs)_2$; results indicate that $Pd(TFA)_2$ and $Pd(CH_3CN)_2(OTs)_2$ could prompt the reaction with lower yields and ee values (Table 1, entries 16-19). Finally, the reaction temperature evaluation indicated that 60 °C is still the best (Table 1, entries 20-21). Thus, the optimal reaction conditions was obtained by using $Pd(OAc)_2$ (10 mol %) as the catalyst, (*4S,4'S*)-4,4'-diisopropyl-2,2'-bis(2-oxazoline) of **L8** (10 mol %) as ligand, 1.1 equiv $T^+BF_4^-$ as the oxidant in 2.5 mL DCE for 0.3 mmol **1a** with 1.2 equiv *para*-methyphenyl boric acid at 60 °C under an argon atmosphere.

To demonstrate the generality of this enantioselective direct C-H oxidation cross-coupling reaction, various substituted substrates were investigated under optimized conditions (Table 2). We first surveyed *N*-*para*-methoxylphenyl protected various glycine esters (Table 2, entries **2a**-**2d**). Although the *tert*-butyl glycine ester gave the 96% ee value, the yield of **2c** was only 31%. Thus, we selected the glycine ethyl ester to react with *para*-methylphenyl boric acid. Investigation of different *N*-aryl groups revealed that the corresponding products of chiral α–amino acids esters were obtained in moderate to good yields with 85-96% ee values (Table 2, entries **2e**-**2j**). **2h** was obtained 81% good yield and relative higher 87% ee value respectively, so we also examined the *N*-*meta*-bromophenyl glycine ethyl ester with some boric acids with the hope of finding the best pattern for the synthesis of chiral α–amino acids esters (Table 2, entries **2k**-**2m**). Indeed, the products were obtained in excellent ee values, but yields were moderate. After summarizing these results, we selected the *N*-*para*-bromophenyl glycine ethyl ester

Table 2. Scope of Synthesis Various Chiral α–Amino acid Esters [a]

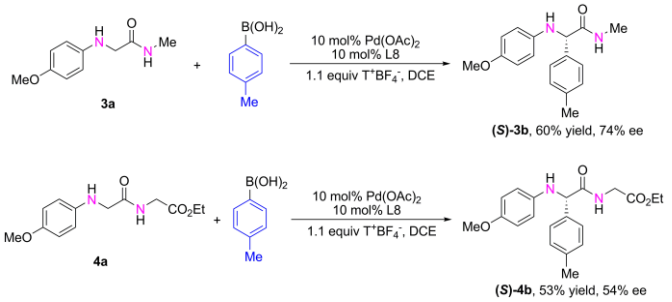


entry	product	yield[b]	ee[c]
2a	R^1 = Et	69%	90% (*S*)
2b	R^1 = Me	60%	91% (*S*)
2c	R^1 = *t*-Bu	31%	96% (*S*)
2d	R^1 = Bn	63%	88% (*S*)
2e		58%	91% (*S*)
2f		40%	96% (*S*)
2g		52%	92% (*S*)
2h		81%	87% (*S*)
2i		85%	85% (*S*)
2j		81%	87% (*S*)
2k		60%	92% (*S*)
2l		53%	90% (*S*)
2m		24%	92% (*S*)
2n		77%	66% (*S*)
2o		67%	86% (*S*)
2p		78%	66% (*S*)
2q	R = CF_3	20%	94% (*S*)
2r	R = $COCH_3$	26%	93% (*S*)
2s	R = CO_2Et	24%	94% (*S*)
2t	R = Ph	70%	90% (*S*)
2u	R = F	62%	87% (*S*)
2v	R = Cl	66%	90% (*S*)
2w	R = Br	69%	90% (*S*)
2x	R = I	71%	94% (*S*)
2y		78%	74% (*S*)
2z		68%	95% (*S*)
2aa		41%	66% (*S*)

[a] Reaction conditions: **1a** (0.3 mmol), boronic acid (1.2 equiv), $Pd(OAc)_2$ (0.1 equiv), L8 (0.1 equiv), $T^+BF_4^-$(1.1 equiv), DCE (2.5 mL) 60 °C under Ar, 16 h. [b] Yield of isolated product. [c] The Enantiomeric excess was determined by chiral HPLC.

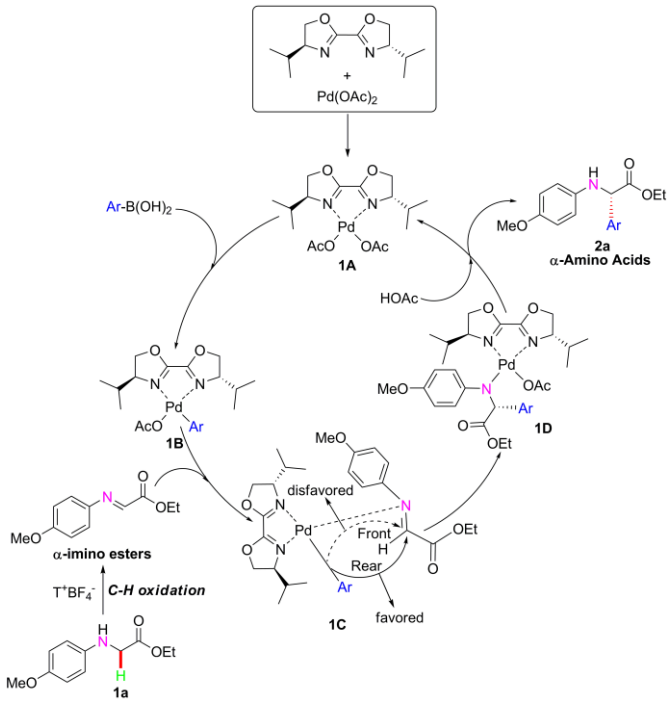
as the substrate to further evaluate different arylboric acids. The steric effect was first examined using the ortho-, *meta*- and *para*-methoxyl phenylboric acids, but results demonstrate its insignificance (Table 2, entries **2n**-**2p**). However, the electronic effect in this transformation was very notable; the strong electronic-deficient groups such as *p*-CF_3, *p*-$COCH_3$, and *p*-CO_2Et phenylboric acids afforded desired products in relative lower yields, but ee values were excellent (Table 2, entries **2q**-**2s**). If phenyl and halogen are the *para*-position substituted groups, the corresponding products of chiral α–amino acids esters are obtained in moderate-to-good yields with 87-94% ee values (Table 2, entries **2t**-**2x**). Furthermore, the benzo [1,3]dioxol-5-ylboronic acid and naphthalen-2-ylboronic acid could also undergo the enantioselective direct C-H oxidative cross-coupling reaction and afford products in good yields with moderate-to-good ee values (Table 2, entries **2y**-**2z**). Of particular note is the heterocycle boric acid, which was also compatible for the reaction; the chiral α–thiophene amino acid ester **2aa** was obtained in 41% yield and 66% ee value (Table 2, entry **2aa**). The relative and absolute configuration of **2z** has been confirmed unequivocally to be (*S*)-**2z** by X-ray diffraction analysis (Figure 1; see the Supporting Information for the details). Those of other adducts were deduced on the basis of this result.

In addition to demonstrate the broad applicability of this catalytic system, we carried out enantioselective direct C-H oxidative cross-coupling of peptide under standard reaction conditions. Corresponding chiral α–arylated peptides were obtained in good yield with moderate ee values (**3b** and **4b**, Scheme 2). We believe that after appropriate optimization of the catalytic system, yields and ee values of the product will increase accordingly. These results indicate that enantioselective direct C-H oxidative cross-coupling reaction provide the best pattern of modification peptide and proteins.



Scheme 2. Enantioselective α–arylated Peptides by Direct C-H Oxidation.

On the basis of the observed experimental results and pioneering reports,[15] we propose a plausible mechanistic pathway outlined in Scheme 3. $Pd(OAc)_2$ first coordinates with the ligand of (*4S,4'S*)-4,4'-diisopropyl-2,2'-bis(2-oxazoline) to form the activated chiral palladium catalyst **1A**, which reacts with aryl boric acid by transmetallation to produce the arylpalladium intermediate **1B**. This active species subsequently attacks the α–imino esters, which has been produced by oxidizing of *N*-aryl glycine ester, because of the coordinating mode of the nitrogen atom of the imine to the palladium center, the aryl group preferred to add to imines from the rear face in a highly selective manner to afford the added product **1D**, which then yielded the product of (*S*)-**2a** upon dissociations, and the active palladium catalyst was regenerated and entered the next catalytic cycle synchronously.



Scheme 3. A Plausible Mechanistic Pathway of Pd(II)-catalyzed Enantioselective C-H Oxidative Cross-coupling.

In conclusion, we have developed a novel pattern for the synthesis of a series of chiral α–amino acid derivatives by palladium-catalyzed enantioselective direct C-H oxidation and arylation reaction. This method also holds significant promise for a potential pathway of enantioselective C_{sp3}–C bond formations by direct C-H oxidative.

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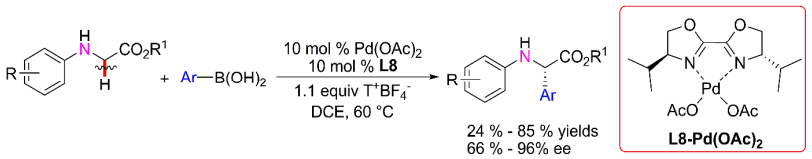

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