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Palladium-catalyzed oxidative cross-coupling for the synthesis of  $\alpha$ -amino ketones<sup>†</sup>

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A novel oxidative cross-coupling reaction for the synthesis of  $\alpha$ -aryl  $\alpha$ -amino ketones in the presence of palladium catalysts using T<sup>+</sup>BF<sub>4</sub><sup>-</sup> as an oxidant has been developed. This transformation was achieved by direct C-H oxidation of  $\alpha$ -aminocarbonyl compounds and arylation. The mild reaction has a broad reaction scope and gives desired  $\alpha$ -aryl  $\alpha$ -amino ketones in moderate to excellent yields.

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Transition metal-catalyzed oxidative coupling reactions involving the formation of C-C bonds from C-H bonds have attracted considerable attention, indicating excellent atom economy and environmental friendliness.<sup>1</sup> α-Amino carbonyl compounds have important roles in natural products and are the key structural units of natural products.<sup>2</sup> These compounds have also been used in organic chemistry to synthesize biological activites, therapeutic agents, quinazolines, imidazoles, pyrazines, indoles, and pyrroles.3 Therefore, the direct oxidative C-H functionalization has gained significant attention for the synthesis of a series of  $\alpha$ -amino carbonyl compounds.<sup>2i,2j,4</sup> For example, Li's group employed an oxidative coupling reaction to synthesize *a*-amino carbonyl compounds from *N*-glycine derivatives by direct C-C bond formation under the catalysis of copper salts.<sup>5</sup> Subsequently, stoichiometric amounts of chemical oxidants, such as DTBP, DDQ, TBHP, and 2,2,6,6tetramethylpiperidine-1-oxoammonium tetra-fluoroborate  $(T^+BF_4^-)$ , have been applied to these reactions.<sup>4a,4d,4p,4t,6</sup> In 2013, Yang's group described a novel protocol for a coppercatalyzed oxidative phosphonation reaction by using a-aminocarbonyls and diphenylphosphine ((1), Scheme 1).7 Huang's group disclosed a general and efficient method for C-N oxidative cross-coupling through direct C<sub>sp3</sub>-H bond functionalization of  $\alpha$ -aminocarbonyl compounds with amines under the catalysis of copper salts ((2), Scheme 1).<sup>6h</sup> In 2015, Yang's group developed a highly efficient route to synthetize chiral arylglycine derivatives via a palladium-catalyzed enantioselective direct C-H oxidation arylation reaction ((3), Scheme 1).<sup>49</sup> Furthermore, transition metal-catalyzed direct C-H functionalization by an oxidative cross-coupling reaction has been reported in the past few years.8 Although significant advances have been made along

these lines, the development of efficient synthetic methodologies for the synthesis of  $\alpha$ -aminocarbonyl compounds *via* palladium-catalyzed oxidative cross-coupling still remains a challenging topic. Based on these considerable progresses, in this paper, we describe a highly efficient C–H oxidative crosscoupling reaction strategy for the synthesis of  $\alpha$ -amino ketone compounds by palladium-catalyzed direct C–H oxidation and arylation reactions ((4), Scheme 1).

In an initial study, we chose 2-((4-chlorophenyl)amino)-1phenylethanone **1a** and *para*-methylphenyl boric acid as the model substrate to evaluate different oxidants in the presence of 10 mol% Pd(OAc)<sub>2</sub> with 2,2-bipyridine as a ligand in TFE at 60 °C (Table 1, entries 1–8). To our delight, the desired product **2a** was obtained in 14% yield by using 2,2,6,6tetramethylpiperidine-1-oxoammonium tetra-fluoroborate (T<sup>+</sup>BF<sub>4</sub><sup>-</sup>)<sup>4p</sup> as an oxidant (Table 1, entry 8). Based on these results, various ligands were used to carry out the reaction in the presence of 10 mol% Pd(OAc)<sub>2</sub>. As expected, the best result of 29% yield was obtained by employing **L**<sub>3</sub> as a ligand (Table 1,



Scheme 1 Transition metal-catalyzed reaction for the synthesis of  $\alpha$ -aminocarbonyl compounds.

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<sup>*a*</sup> Reaction conditions: 1a (0.1 mmol), *para*-methyphenyl boric acid (1.2 equiv.), catalyst (10 mol%), ligand (10 mol%) and oxidant (1.2 equiv.) was stirred in solvent (1 mL) at 60 °C under Ar for 20 h. <sup>*b*</sup> Yield of the isolated product. <sup>*c*</sup> 100 °C. <sup>*d*</sup> 80 °C.

To our delight, the reaction could occur in the presence of 10 mol% of catalysts such as  $Pd(NO_3)_2$ ,  $Pd(TFA)_2$ ,  $PdCl_2$ ,  $Pd(PPh_3)_2Cl_2$ ,  $Pd(PPh_3)_4$ ,  $Pd(CH_3CN)_2Cl_2$ , and  $Pd(acac)_2$ , while the reactivity of  $Pd(PCy_3)_2Cl_2$  was better than others, affording the desired product **2a** in 86% yield (Table 1, entries 28–37). Furthermore, control experiments showed that no or trace amounts of the desired product was obtained in the absence of  $Pd(PCy_3)_2Cl_2$  or  $T^+BF_4^-$  (Table 1, entries 38 and 39).

With the optimal reaction conditions in hand (Table 1, entry 37), we explored the C-H oxidative cross-coupling reaction of 2-((4-chlorophenyl)amino)-1-phenylethanone 1a with arylboric acids, as shown in Table 2. We first surveyed different substituents of arylboric acids with electron-donating groups, such as methyl, ethyl, isopropyl and methoxy, and found that they gave the desired product in 80-86% yields (Table 2, entries 2a-2d). Meanwhile, the steric effect was examined using the meta- and ortho-methyl phenylboric acids under identical conditions (Table 2, entries 2e and 2f). However, the steric effect in this transformation was very significant; only trace amounts of the product was obtained when ortho-methyl phenylboric acids were introduced for the optimization of reaction conditions (Table 2, entry 2f). When arylboric acids with different electrondonating or electron-withdrawing groups afforded the desired products in excellent to moderate yields (Table 2, entries 2g-

 Table 2
 Reaction conditions screening<sup>a,b</sup>



entries 9–15). Then, different solvents were screened; using  $CH_3OH$  as the solvent with the set reaction conditions gave comparable results (entry 25), but others gave lower yields (Table 1, entries 16–25). When the temperature was increased to 80 °C, the yield of **2a** reached 71% (Table 1, entries 26 and 27).

<sup>*a*</sup> Reaction conditions: **1a** (0.1 mmol), *para*-methyphenyl boric acid (1.2 equiv.), Pd(PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10 mol%), and 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetra-fluoroborate ( $T^+BF_4^-$ ) (1.2 equiv.) was stirred in CH<sub>3</sub>OH (1 mL) at 80 °C under Ar for 20 h. <sup>*b*</sup> Yield of the isolated product. <sup>*c*</sup> Potassium phenyltrifluoroborate as arylated reagents.



Scheme 2 Radical-trapping experiment.

**2m**). Moreover, in order to further expand the substrate scope, we selected potassium phenyltrifluoroborate as the arylated reagent under the optimized reaction conditions; the corresponding  $\alpha$ -alkylation product **2i** was obtained in 45% yield (Table 2, entry **2i**).

Furthermore, the naphthalen-1-ylboronic acid and benzo [1,3]dioxol-5-ylboronic acid could also afford  $\alpha$ -aminocarbonyl compounds **2n** and **2o** in 73–77% yields (Table 2, entries **2n** and **2o**). Of particular note is the heterocyclic boronic acid, which was also compatible for the reaction (Table 2, entries **2p** and **2q**). Moreover, the introduction of various electron-withdrawing or electron-donating substituents on the aniline moeity gave the corresponding  $\alpha$ -aminocarbonyl compounds in 30–88% yields (Table 2, entries **2r–2x**); the electronic effect and the steric effect in this transformation was very notable (Table 2, entries **2t–2v**). Next, different substituent groups of  $\alpha$ -carbonyl compounds bearing different functional groups were additionally examined and the corresponding products were generated in moderate yields (Table 2, entries **2y** and **2z**).

To investigate the mechanism of this transformation, experiments were carried out. The desired product was obtained in the range of 86% to 65% and 86% to 45% yield when 2.0 equivalents of radical-trapping reagents 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were used, respectively, under standardized reaction conditions (Scheme 2). To our delight, the key  $\alpha$ -imino intermediate **A** was detected by GC-MS (see ESI†). Based on the observed experimental results and pioneering reports,<sup>4p,9</sup> we have described a plausible mechanistic pathway in Scheme 3. Initially, the arylpalladium intermediate **B** was produced *via* a transmetallation reaction of Pd(PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> with aryl boric acid, which attacks the  $\alpha$ -imino intermediate **A** obtained by the *in situ* oxidation of **1a** by T<sup>+</sup>BF<sub>4</sub><sup>-</sup> to form the complex **C**. Then, an aryl group was added to the imine to generate intermediate **D**.

Scheme 3 Proposed mechanism.

Finally, the product **2a** was obtained upon dissociation in the presence of  $H^+$ . At the same time, the palladium catalyst was regenerated and synchronized into the next catalytic cycle (Scheme 3).

In summary, we have achieved a novel pattern for the synthesis of  $\alpha$ -aryl  $\alpha$ -amino ketone compounds *via* Pd(II)-catalyzed oxidative coupling of  $\alpha$ -aminocarbonyl compounds with arylboric acids. This reaction occurs *via* direct C–H oxidation and arylation reactions. The coupling of  $\alpha$ -aminocarbonyl compounds gave functionalized  $\alpha$ -aryl  $\alpha$ -amino ketone compounds in moderate to excellent yields.

### Conflicts of interest

There are no conflicts to declare.

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