Palladium-catalyzed oxidative cross-coupling for the synthesis of \( \alpha \)-amino ketones†

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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 \( \text{T}^+ \text{BF}_4^- \) 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.

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. \( \alpha \)-Amino carbonyl compounds have important roles in natural products and are the key structural units of natural products. These compounds have also been used in organic chemistry to synthesize biological activities, therapeutic agents, quinazolines, imidazoles, pyrazines, indoles, and pyrroles. Therefore, the direct oxidative C–H functionalization has gained significant attention for the synthesis of a series of \( \alpha \)-amino carbonyl compounds. For example, Li’s group employed an oxidative coupling reaction to synthesize \( \alpha \)-amino carbonyl compounds from \( N \)-glycine derivatives by direct C–C bond formation under the catalysis of copper salts. Subsequently, stoichiometric amounts of chemical oxidants, such as DTBP, DDQ, TBHP, and 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetra-fluoroborate (\( \text{T}^+ \text{BF}_4^- \)), have been applied to these reactions. In 2013, Yang’s group described a novel protocol for a copper-catalyzed oxidative phosphonation reaction by using \( \alpha \)-aminocarboxyls and diphenylphosphine ((1), Scheme 1). Huang’s group disclosed a general and efficient method for \( C-N \) oxidative cross-coupling through direct C–C bond functionalization of \( \alpha \)-aminocarboxyl compounds with amines under the catalysis of copper salts ((2), Scheme 1). In 2015, Yang’s group developed a highly efficient route to synthesize chiral arylglycine derivatives via a palladium-catalyzed enantioselective direct C–H oxidation arylation reaction ((3), Scheme 1). Furthermore, transition metal-catalyzed direct C–H functionalization by an oxidative cross-coupling reaction has been reported in the past few years. 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 cross-coupling 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-\((4\text{-chlorophenyl})\text{amino}\)\(-1\)-phenylethanone 1a and \( \text{para} \)-methylphenyl boric acid as the model substrate to evaluate different oxidants in the presence of 10 mol% \( \text{Pd(OAc)}_2 \), 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 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetra-fluoroborate (\( \text{T}^+ \text{BF}_4^- \)) 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% \( \text{Pd(OAc)}_2 \). As expected, the best result of 29% yield was obtained by employing \( \text{L}_3 \) as a ligand (Table 1,

\[ \text{Scheme 1} \quad \text{Transition metal-catalyzed reaction for the synthesis of} \quad \alpha \text{-aminocarbonyl compounds.} \]

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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$_3$)$_2$Cl$_2$, Pd(PPh$_3$)$_4$, Pd(CH$_2$CN)$_2$Cl$_2$, and Pd(acac)$_2$, while the reactivity of Pd(PCy$_3$)$_2$Cl$_2$ 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$_3$)$_2$Cl$_2$ or T$^\text{BF}_4$ (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 electron-donating or electron-withdrawing groups afforded the desired products in excellent to moderate yields (Table 2, entries 2g–

Table 1 Optimization of the reaction conditions$^{a,b}$

| Entry | Catalyst | Ligand | Oxidant | Solvent | Yield$^b$ |
|-------|----------|--------|---------|---------|----------|
| 1     | Pd(OAc)$_2$ | bpy    | BQ      | TFE     | 10%      |
| 2     | Pd(OAc)$_2$ | bpy    | Ag$_2$CO$_3$ | TFE     | 13%      |
| 3     | Pd(OAc)$_2$ | bpy    | K$_3$S$_2$O$_8$ | TFE     | Trace    |
| 4     | Pd(OAc)$_2$ | bpy    | Air     | TFE     | 8%       |
| 5     | Pd(OAc)$_2$ | bpy    | PhI(OAc)$_2$ | TFE     | Trace    |
| 6     | Pd(OAc)$_2$ | bpy    | Ph$_2$CBF$_3$ | TFE     | NR       |
| 7     | Pd(OAc)$_2$ | bpy    | C$_2$H$_4$BF$_4$ | TFE     | Trace    |
| 8     | Pd(OAc)$_2$ | t$_2$ | T$^\text{BF}_4$ | TFE     | 14%      |
| 9     | Pd(OAc)$_2$ | L$_1$  | T$^\text{BF}_4$ | TFE     | 24%      |
| 10    | Pd(OAc)$_2$ | L$_2$  | T$^\text{BF}_4$ | TFE     | 13%      |
| 11    | Pd(OAc)$_2$ | L$_1$  | T$^\text{BF}_4$ | TFE     | 29%      |
| 12    | Pd(OAc)$_2$ | L$_4$  | T$^\text{BF}_4$ | TFE     | 15%      |
| 13    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | TFE     | 20%      |
| 14    | Pd(OAc)$_2$ | L$_2$  | T$^\text{BF}_4$ | TFE     | 12%      |
| 15    | Pd(OAc)$_2$ | L$_2$  | T$^\text{BF}_4$ | DCE     | 16%      |
| 16    | Pd(OAc)$_2$ | L$_1$  | T$^\text{BF}_4$ | THF     | 31%      |
| 17    | Pd(OAc)$_2$ | L$_1$  | T$^\text{BF}_4$ | TOL     | Trace    |
| 18    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$NO$_2$ | 16 |
| 19    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | DCM     | 18%      |
| 20    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | C$_2$H$_5$OH | 37% |
| 21    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | DME     | 40%      |
| 22    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | DMF     | 8%       |
| 23    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | Dioxane | 32%      |
| 24    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$OH | 47%      |
| 25    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$OH | 23%      |
| 26    | Pd(OAc)$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$OH | 71%      |
| 27    | Pd(NO$_3$)$_2$ | L$_1$  | T$^\text{BF}_4$ | CH$_3$OH | 56%      |
| 28    | Pd(NO$_3$)$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$OH | 43%      |
| 29    | Pd(TFA)$_2$ | L$_1$  | T$^\text{BF}_4$ | CH$_3$OH | 67%      |
| 30    | Pd(TFA)$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$OH | 60%      |
| 31    | Pd(PPh$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 30%      |
| 32    | Pd(PPh$_3$)$_4$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 74%      |
| 33    | Pd(CH$_2$CN)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 58%      |
| 34    | Pd(acac)$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 63%      |
| 35    | Pd(PPh$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 66%      |
| 36    | Pd(PPh$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 86%      |
| 37    | Pd(PCy$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | Trace    |
| 38    | Pd(PCy$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | No       |

$^a$ Reaction conditions: 1a (0.1 mmol), para-methylphenyl 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. $^b$ Yield of the isolated product. $^c$ 100 °C. $^d$ 80 °C.

Table 2 Reaction conditions screening$^{a,b}$

| Entry | Catalyst | Oxidant | Solvent | Yield$^b$ |
|-------|----------|---------|---------|----------|
| 1     | Pd(NO$_3$)$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$OH | 43%      |
| 2     | Pd(TFA)$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$OH | 67%      |
| 3     | PdCl$_2$ | L$_3$  | T$^\text{BF}_4$ | CH$_3$OH | 60%      |
| 4     | Pd(PPh$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 30%      |
| 5     | Pd(PPh$_3$)$_4$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 74%      |
| 6     | Pd(CH$_2$CN)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 58%      |
| 7     | Pd(acac)$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 63%      |
| 8     | Pd(PPh$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 66%      |
| 9     | Pd(PPh$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | 86%      |
| 10    | Pd(PCy$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | Trace    |
| 11    | Pd(PCy$_3$)$_2$Cl$_2$ | L$_3$ | T$^\text{BF}_4$ | CH$_3$OH | No       |

$^a$ Reaction conditions: 1a (0.1 mmol), para-methylphenyl boric acid (1.2 equiv.), Pd(PCy$_3$)$_2$Cl$_2$ (10 mol%), and 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetra-fluoroborate (T$^\text{BF}_4$) (1.2 equiv.) was stirred in CH$_3$OH (1 mL) at 80 °C under Ar for 20 h. $^b$ Yield of the isolated product. $^c$ Potassium phenyltrifluoroborate as arylated reagents.
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 moiety 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 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,4c–e we have described a plausible mechanistic pathway in Scheme 3. Initially, the arylpalladium intermediate B was produced via a transmetallation reaction of \( \text{Pd(PCy}_3\text{)}_2\text{Cl}_2 \) with aryl boric acid, which attacks the \( \alpha \)-imino intermediate A obtained by the \textit{in situ} oxidation of \( 1a \) by \( \text{T}^+\text{BF}_4^- \) to form the complex C. Then, an aryl group was added to the imine to generate intermediate D. Finally, the product \( 2a \) was obtained upon dissociation in the presence of \( \text{H}^+ \). 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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