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A highly efficient Pd-catalyzed decarboxylative ortho-arylation of amides with aryl acylperoxides

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An efficient Pd-catalyzed decarboxylative ortho-arylation of amides with aryl acylperoxides was developed. A variety of anilides reacted with aryl acylperoxides to afford the corresponding ortho-arylation products, and N-methoxyarylamides generated phenanthridinones.

During the past decades, the transition-metal-catalyzed functionalization of C–H bonds has emerged as a powerful tool in organic synthesis. Many versatile and flexible methodologies have been made to activate C–H bonds, in particular aromatic ones for the synthesis of complicated natural products, drugs and advanced materials from simple and commercially available chemicals.1 With the assistance of an ortho-position directing group in C–H activation, a highly efficient and regio-selective functionalization could be achieved.2 A wide variety of functional groups,3−9 such as anilides,3 amides,4 pyridines/quinolones,5 oximes,6 carboxylic acids,7 ketones,8 N-methoxy amides,9 have been developed as directing groups. Among them, directed ortho-arylation to construct biaryl skeleton has gained significant attention because the biaryl linkages constitute a valuable class of important structural units.10 It showed that Ru, Rh, Pd, Cu or other transition metal complexes are efficient catalysts for the direct arylation of aromatic C–H bonds using arenes which are functionalized with boron, halides or other organometals.11 However, their relatively high price and complicated preparation would reduce their potential applications in organic synthesis.

Most recently, the utilization of non-toxic and low cost carboxylic acids for decarboxylative arylations is an attractive development in this area.12 It accesses reactive organometallic intermediates through the removal of CO₂ without using prefunctionalized substrates comparing to traditional cross-coupling methods. The representative examples of decarboxylative arylation cross-couplings are developed by Goossen,13 Forgione,14 Myers,15 Liu and Fu,16 Su,17 et al.18 However, high reaction temperature and long reaction time could not be avoided in most cases.

In 2009, Yu demonstrated a direct decarboxylative ortho-arylation of 2-phenylpyridines with benzoyl peroxides in the presence of a Pd-complex with good reactivity and selectivity for the synthesis of arylated derivatives.19 It is the first utilization of directing groups in decarboxylative cross-coupling using a peroxide as substrate (Scheme 1).20,21 In our continuing efforts on the sp² C–H activation using directing groups to construct C–C bonds,22 herein, we will report that Pd-catalyzed direct arylation of anilides using aryl acylperoxides afforded the corresponding ortho-arylation products, and the reaction of N-methoxyarylamides with aryl acylperoxides generated the phenanthridinones (Scheme 1).
In our initial study, we focused on N-phenylpivalamide (1a), shown relatively high reactivity, and benzoyl peroxide (2a) as the model substrates to screen the optimal reaction conditions. Treatment of 1a with 2a in the presence of Pd(OAc)$_2$ (7.5 mol%), and TfOH (2.0 equiv) in CH$_2$CN (2.0 mL) at 80 °C for 32 h, providing the desired product 3a in 53% yield (Table S1, ESI†). It is noteworthy that the yield of 3a could be improved to 77% significantly, when activated 3Å molecular sieves was added to the reaction, but 4Å molecular sieves was inferior.  To optimize the reaction conditions, various additives, temperature and solvents were examined. Our investigation indicated that no desired product was obtained when the model reaction was performed in the absence of TfOH or in the presence of a base, such as K$_2$CO$_3$ or Na$_2$CO$_3$ (Table S1, ESI†), and TfOH is crucial for the reaction. Other acids including TFA, HOAc, and pivalic acid were also surveyed, but they were all ineffective. When p-TsOH and CH$_2$SO$_2$H were used in the model reaction, 3a was obtained in 31% and 35% yields, respectively. It was also found that the optimized amount of TfOH is 2.0 equiv. The reaction temperature and time were also examined and the reaction generated the desired product in highest yield at 80 °C for 32 h. The control experiments also showed that the reaction did not proceed in the absence of Pd and the Pd amount was found to be 7.5 mol%. Use of other Pd-catalysts, such as Pd(TFA)$_2$, PdCl$_2$, Pd(PPh$_3$)$_2$Cl$_2$, Pd(PPh$_3$)$_2$ led to the lower yields of 3a compared with Pd(OAc)$_2$. In addition, the effect of solvent was explored. Toluene, DCE, 1,4-dioxane, DMF, DMSO, DME or HOAc/CH$_2$CN were employed instead of CH$_2$CN, poor yields of 3a were observed (Table S1, ESI†). Therefore, the optimized reaction conditions were Pd(OAc)$_2$ (7.5 mol%), TfOH (2.0 equiv) and 3Å molecular sieves in CH$_2$CN at 80 °C for 32 h.

With the optimized reaction conditions in hand, the effect of N-substituents on the anilides including acetanilide (1b), N-phenylbutyramide (1c), N-phenylbenzamide (1d), 1-phenylpyrrolidin-2-one (1e), N-acetyl-2,3-dihydroindole (1f) and 1,1-dimethyl-3-phenylurea (1g) was studied and the results are shown in Scheme 2. Gratifyingly, most of them reacted with 2a to generate the corresponding products (3b–3e) in 50–69% yields. However, 1f and 1g failed to react with 2a. It showed that pivalamide was the best one for the arylation.

Under the optimized reaction conditions, the substrate scope of N-aryl pivalamides (1) and aryl acylperoxides (2) was investigated to illustrate the efficiency of this strategy (Scheme 3). N-Aryl pivalamides with various substituents (Me, i-Pr, OMe, F, Cl, Br) on the benzene rings were explored. Pivalamides bearing electron-donating groups at meta- and/or para-positions of the phenyl rings (1h, 1i, 1k, 1l and 1p) underwent the decarboxylative ortho-arylation smoothly to generate the corresponding products (3h, 3i, 3k, 3l and 3p, Scheme 3) in 61–81% yields. An obvious ortho-substituent effect was observed in the reaction of 2-methyl substituted pivalamide 1j with 2a. However, the substrates bearing electron-withdrawing groups (3-F, 3-Cl, 3-Br) reacted with 2a under the standard reaction conditions, but failed. When the reactions were performed with addition of K$_2$S$_2$O$_5$ (2.0 equiv) at 130 °C, the desired ortho-arylation products (3m, 3n, and 3o) were obtained in 33–41% yields. Whereas the phenyl ring in 1 was instead of 1-naphthyl (1q), it provided 3q in 50% yield.

To further expand the substrate scope, we performed the present arylation of N-(m-tolyl)pivalamidine (1i) with a variety of aryl acylperoxides (2b–2j), and the results are also shown in Scheme 3. Substituted groups, such as 4-methyl-, 4-fluoro-, 3-chloro-, 4-chloro-, 4-bromo-, and 4-tert-butylphenyl acylperoxides underwent the coupling with 1i smoothly, giving the coupling products 3r–3u, 3w and 3x in 55–75%, 59% and 47% yields, respectively. An ortho-substituent effect was also found during the formation of 3v in 36% yield. However, neither the strong electron-withdrawing (p-NO$_2$) nor the strong electron-donating group (p-CH$_3$O) could be functionalized to generate the desired product in the reaction with starting materials unchanged and recovered (3y and 3z).

With the obtained 3b in hand, its transformation through an intramolecular cyclization under Buchwald amination conditions was examined, providing carbazole 4b in 91% yield (Scheme 4).
Subsequently, other amide substrates were carried out for the purpose of broadening the application of current methodology. A series of amides, such as benzamide, N-iso-propylbenzamide, N-tosy1benzamide were used for the reaction with benzoyl peroxide, but failed. Much to our pleasure, N-methoxybenzamide (5a) was found to be a promising coupling partner in the reaction, providing an aryl-arylation-product phenanthridinone (6a), as an important structural motif in numerous biologically molecules, summarized in Scheme 5. A variety of amides, such as benzamide, phenyl (Ph), and methoxy (MeO) at the para-position of the phenyl rings gave the comparable product yields to non-substituted one (N-methoxybenzamide, 5a). To further expand the substrate scope, some aryl acy1peroxides, including 4-methylphenyl acy1peroxide, 4-chlorophenyl acy1peroxide, and 4-bromophenyl acy1peroxide, were used to react with 5a, providing the corresponding products (6j-6l) in 35-57% yields.

In summary, a highly efficient palladium-catalyzed decarboxylative ortho-arylation of amides with aryl acy1peroxides via C-H activation and functionalization was developed. This synthetic methodology provides a simple and direct route to a wide variety of diversely ortho-functionalized biaryl compounds from anilides, and phenanthridinones from N-methoxybenzamides through an arylation-cyclization process. The further investigation is currently underway. This work was financially supported by the National Science Foundation of China (No. 21172092).

Notes and reference


