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Redox-Neutral Palladium-Catalyzed C−H Functionalization To Form Isoindolinones with Carboxylic Acids or Anhydrides as Readily Available Starting Materials

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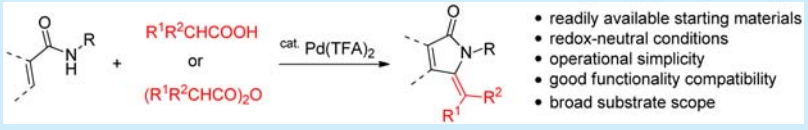
Supporting Information



ABSTRACT: An operationally simple, Pd-catalyzed C−H functionalization is described for the synthesis of important and useful isoindolinones from readily available carboxamides and carboxylic acids or anhydrides. The reactions proceed efficiently with a broad range of substrates under redox-neutral reaction conditions and tolerate a diversity of functional groups. The mechanistic investigation suggests that the reactions involve C−H activation, nucleophilic addition, β-O elimination, and dehydration steps.

Transition-metal-mediated C−H functionalization has emerged as a useful, atom- and step-economic synthetic protocol to construct a number of important *N*-heterocycles.[1] In this context, the synthesis of isoindolinones has attracted considerable attention owing to their interesting biological and pharmaceutical properties,[2] as well as their usefulness as precursors for the synthesis of structurally diverse and complex molecules (Figure 1).[3] Several methods have successfully been

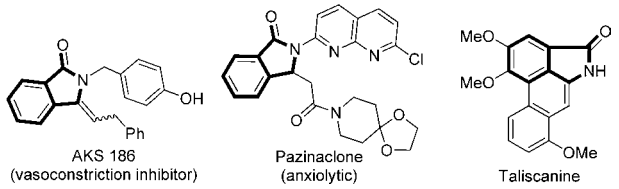


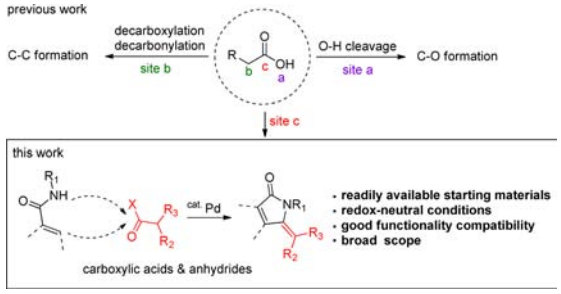
Figure 1. Representative isoindolinones with biological and pharmaceutical properties.

developed toward the isoindolinone synthesis based on Pd,[4] Cu,[5] Ru,[6] Rh,[7] and Re[8] salts. Among these reactions, the oxidative coupling reactions of benzamides with alkenes[4,6,7a−d,h−k] or alkynes[5a] exhibited high atom economy. However, all the reactions required the use of excess oxidants including benzoquinone, $Cu(OAc)_2$, or Ag_2CO_3, thus generating stoichiometric amounts of undesired wastes. Furthermore, the existence of oxidants may make the functional groups that are sensitive to oxidation incompatible under the oxidative reaction conditions.

Carboxylic acids are commercially available in a large structural variety, and they can also be easily prepared by numerous methods.[9] These compounds are easy to store and simple to handle. Thus, the carboxylic acids are extremely attractive raw materials for organic synthesis. Many recent reports have shown the versatility of these reagents in the transition-metal-mediated cross-coupling reactions.[10] For example, arylcarboxylic acids are good surrogates of aryl organometallic reagents for biaryl synthesis.[10a] Yet, the carboxylic acids have also displayed good reactivity in the C−H functionalization for the construction of C−O and C−C bonds.[11] Most of the reactions occurred either at the OH position of the COOH involving O−H cleavage[11a,h,i] or at the α-C position connected with the COOH involving decarboxylation or decarbonylation (Scheme 1).[11b,c,e,f,m] Nevertheless, only a few examples of C−C bond formation occurring at the C═O of the COOH have been realized.[11j,l]

The ready availability of the carboxylic acids and our interests in the C−H activation[12] led us to consider using these reagents in the C−H functionalization to construct the valuable isoindoli-

Scheme 1. Different Pathways of Carboxylic Acids in Transition-Metal-Mediated C−H Functionalization



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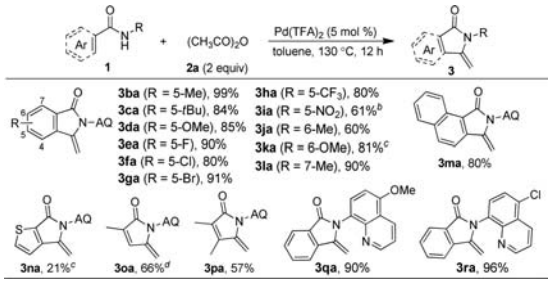
nones. We can envision that the abundance and structural diversity of the carboxylic acids as well as the merits of C−H functionalization would make the synthetic methods desirable and attractive. Herein, we disclose an efficient Pd-catalyzed C−H functionalization/annulation approach for the expedient assembly of the isoindolinone rings from readily available carboxamides and carboxylic acids or anhydrides (Scheme 1). This approach features redox-neutral conditions, operational simplicity, a wide ranging substrate scope, and tolerance of various synthetically useful functional groups.

Since most carboxylic acids can be easily transformed into their anhydrides,[13] our first goal was the development of an effective catalytic system capable of the realization of the isoindolinone synthesis with anhydrides as coupling partners. We chose the reaction between benzamide **1a** and commercially available acetic anhydride **2a** as a model system to optimize the reaction conditions. After considerable experimentation, we found that the reaction proceeded smoothly with $Pd(TFA)_2$ (5 mol %) in toluene at 130 °C for 12 h, affording the target product **3aa** in 99% yield (see Supporting Information (SI) for detailed results of the reaction optimization). In this reaction, aminoquinoline (AQ)[14] was employed as a bidentate directing group to assist the *ortho* C−H cleavage. Besides, 2-(pyridine-2-yl)propan-2-amine developed by Shi[15] also acted as an effective directing group, delivering the target product in 82% yield. However, other substituents such as naphthyl, acetyl, and methyl groups showed no efficiency (see SI for detailed results). Notably, a mixture of **1a** (10 mmol, 2.48 g), **2a** (20 mmol, 2.04 g), and $Pd(TFA)_2$ (0.5 mmol, 0.17 g) in toluene was stirred at 130 °C for 12 h to furnish 2.67 g of **3aa** (98% yield), indicating the good scalability of our method.

With the optimal reaction conditions in hand, we next explored the substrate scope with respect to the aromatic and olefinic carboxamides. As shown in Scheme 2, a series of

Scheme 2. Substrate Scope of Aromatic and Olefinic Carboxamides[a]

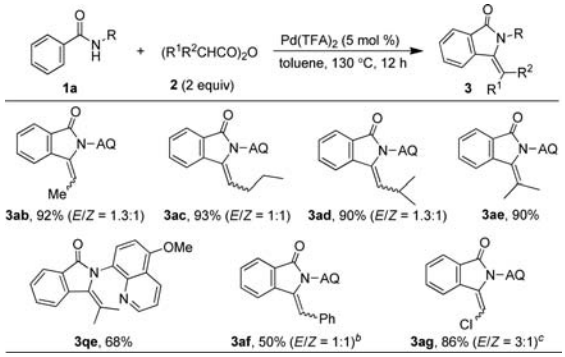


[a]Reaction performed on a 0.2 mmol scale under Ar. Isolated yields are indicated. AQ = aminoquinoline. [b]**2a** (7 equiv), $Pd(TFA)_2$ (20 mol %). [c]$Pd(TFA)_2$ (10 mol %). [d]**2a** (5 equiv), $Pd(TFA)_2$ (20 mol %).

benzamides efficiently reacted with **2a** to deliver the corresponding isoindolinones in good to excellent yields (**3ba**−**3ma**). A variety of electron-donating and -withdrawing groups were tolerated, including synthetically important fluoro (**3ea**), chloro (**3fa**), bromo (**3ga**), trifluoromethyl (**3ha**), and nitro groups (**3ia**). It was noted that the reactions exclusively occurred at the less hindered site for *m*-methyl and -methoxy substituted benzamides (**3ja** and **3ka**). A thiophene-derived amide also reacted with **2a** although it only gave **3na** in 21% yield. Presumably, the strong coordination property of the sulfur atom reduced the catalytic ability of the Pd. Moreover, not only the aromatic carboxamides but also the olefinic carboxamides were amenable to the reactions; thus, the desired products **3oa** and **3pa** were produced in 66% and 57% yields, respectively. The electron-donating methoxy group and elelctron-withdrawing chloro group on the quinoline ring almost did not affect the transformations, which were indicated by the results of **3qa** and **3ra**.

Subsequently, we explored the scope of the anhydrides to further enrich the structural diversity of the isoindolinones (Scheme 3). Gratifyingly, commercially available anhydrides,

Scheme 3. Substrate Scope of Anhydrides[a]



[a]Reaction performed on a 0.2 mmol scale. Isolated yields are indicated. AQ = aminoquinoline. [b]$Pd(TFA)_2$ (10 mol %). [c]Anhydride (5 equiv).

such as propionic, valeric, isovaleric, and isobutyric anhydrides, all displayed good reactivity. Thus, the reactions efficiently furnished the corresponding products bearing alkyl groups at the terminal olefinic position (**3ab**−**3ae** and **3qe**). In addition, the isoindolinones with phenyl and chloro substitutions at the terminal olefinic position were also obtained in moderate to good yields (**3af** and **3ag**). Unfortunately, benzoic anhydride, formic anhydride, and crotonic anhydride were unreactive in the reactions.

Given the much wider variety and better stability of the carboxylic acids than those of the anhydrides, we thought to explore the direct use of the carboxylic acids as the coupling partners to realize the construction of the isoindolinone rings (Scheme 4). We conceived that the key point to realize such reactions was to identify a suitable additive to activate the less reactive carboxylic acids. To this end, different activators including benzoyl chloride (PhCOCl), pivaloyl chloride (*t*BuCOCl), trifluoroacetic anhydride [$(CF_3CO)_2O$], *tert*-butyldicarbonate (Boc_2O), and pivalic anhydride [$(t$BuCO$)_2O$] were investigated for the reaction between **1a** and tetrahydropyran-4-carboxylic acid **2h**. We found that the reactions gave rise to the desired product **3ah** in moderate to good yields in the presence of Boc_2O (63%), $(CF_3CO)_2O$ (81%), and $(t$BuCO$)_2O$ (89%), while PhCOCl and *t*BuCOCl showed very low promotion to the reaction (<5% yield). After establishing the beneficial effect of $(t$BuCO$)_2O$, we then probed the scope of the carboxylic acids. Cyclic aliphatic acids with five-, six-, and seven-member rings all reacted well with **1a**, generating the target products in good yields (**3ai**−**3ak**). Interestingly, *N*-heterocyclic and fluorene functionalities were compatible with the reactions (**3al** and **3am**). It was notable that phenylacetic acid exhibited excellent reactivity in the reaction with **1a**, which afforded **3af** in 83% yield, better than the reaction using 2-phenylacetic anhydride as the coupling partner (50% yield, Scheme 3). Similarly, 3,3,3-trifluoropropionic acid, 3-phenylpropanoic acid,

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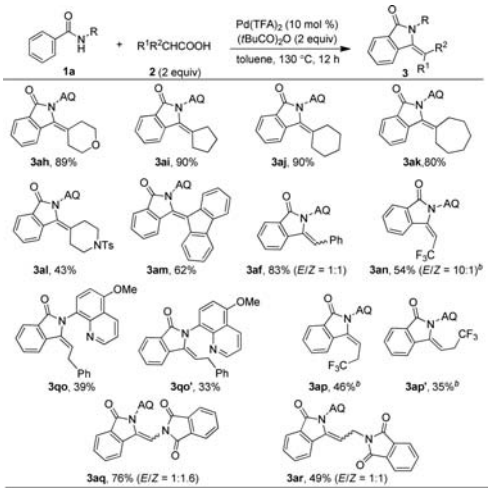
Scheme 4. Substrate Scope of Carboxylic Acids[a]



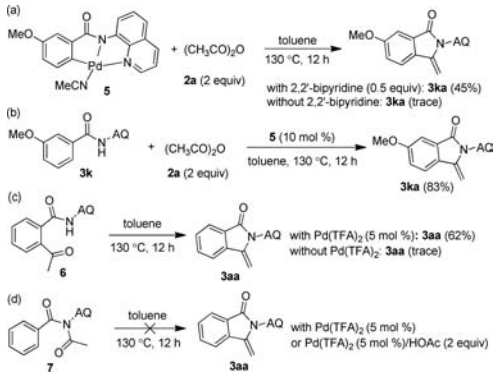
[a]Reaction performed on a 0.2 mmol scale under Ar. Isolated yields are indicated. AQ = aminoquinoline. [b]$Pd(TFA)_2$ (20 mol %) and carboxylic acid (4 equiv).

and 4,4,4-trifluorobutyric acid were also competent substrates in the reactions (**3an**, **3qo**, **3qo′**, **3ap**, and **3ap′**). It is noteworthy that **3qo** is an analogue of AKS 186, which is a potential inhibitor of the thromboxane A_2 analogue (U-46619)-induced vasoconstriction.[2g] Significantly, amino acids such as *N*-phthaloyl-protected glycine and *β*-alanine also served as suitable coupling partners in the isoindolinone synthesis and provided the corresponding products in synthetically useful yields (**3aq** and **3ar**).

We next performed a series of kinetic isotope effect and competition experiments (see SI for detailed results). The results of the H/D exchange experiment between **1a** and 10 equiv of deuterium oxide showed that 88% D was introduced into the two *ortho* positions of the benzamide aryl ring, suggesting that the C−H cleavage step is reversible. The intermolecular competition reaction between **1a** and its pentadeuterated **1a**-d_5 showed a modest KIE of 1.7. On the other hand, comparison of parallel independent reactions of **1a** and **1a**-d_5 also exhibited a modest KIE of 1.6. These observations might indicate that the C−H cleavage is not involved in the rate-limiting step of the reaction.[16] Moreover, the unsymmetric anhydride **4** generated from phenylacetyl chloride and sodium acetate was used to react with **1a** to probe the reaction selectivity, which favored the formation of **3aa** as the major product.

To gain more insight into the possible mechanism, several experiments were further carried out (Scheme 5). A cyclopalladium intermediate resulting from the C−H activation was supported in the present reaction. Thus, the reaction of acetic anhydride **2a** and **5**[17] in the presence of 0.5 equiv of 2,2′-bipyridine afforded **3ka** in 45% yield (Scheme 5a). Only a trace amount of **3ka** was observed in the absence of the 2,2′-bipyridine. The 2,2′-bipyridine likely acted as a ligand, due to its strong coordination ability, to exclude the acetonitrile bonded with palladium to form a new intermediate. Moreover, the cyclopalladium species served as a catalyst for the coupling reaction between **3k** and **2a**, delivering **3ka** in 83% yield (Scheme 5b). In addition, a compound **6** with an acetyl group at the *ortho* position was investigated toward **3aa** formation (Scheme 5c). The desired product was formed in 62% yield with 5 mol % of $Pd(TFA)_2$, while a trace amount of **3aa** was observed without the catalyst. In

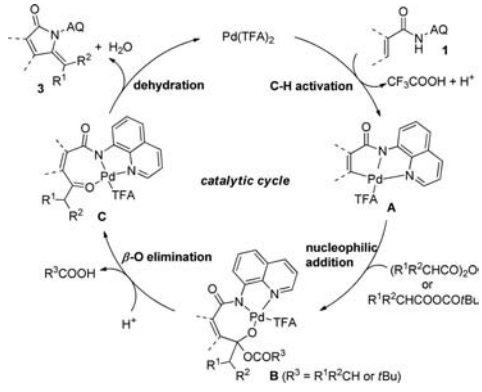
Scheme 5. Mechanistic Experiments



addition, other additives, such as $Cu(OTf)_2$, $Zn(OTf)_2$, $Mg(OTf)_2$, $InCl_3$, $AuCl_3$, HOAc, and PivOH, were also tested; however, no desired product was observed. These results indicated, in large part, that the desired isoindolinone was formed from an *ortho*-acylated compound, and this process needed the participation of $Pd(TFA)_2$. It should be noted that a compound **7** with an acetyl group at the N atom cannot be converted into **3aa** in the presence of $Pd(TFA)_2$ or $Pd(TFA)_2$/HOAc, which precluded the involvement of such an intermediate in the reaction (Scheme 5d).

Based on the above preliminary mechanistic results, we suggest a possible catalytic cycle as depicted in Scheme 6. The

Scheme 6. Possible Catalytic Cycle



reaction is initiated by palladium(II)-mediated and aminoquinoline-directed C−H activation. The resulting palladacycle (II) intermediate **A** reacts with anhydride to form an intermediate **B** through a nucleophilic addition process.[18] Subsequently, the intermediate **B** is prone to *β*-oxygen elimination, furnishing an intermediate **C** that occurs via intramolecular dehydration to generate the desired product **3**.[19]

In conclusion, we have developed an efficient, operationally simple, and scalable palladium-catalyzed C−H functionalization for the synthesis of isoindolinones from readily available carboxamides and carboxylic acids or anhydrides. This protocol shows wide substrate scope and good functional group compatibility. Moreover, this practical method would not only complement existing synthetic methods but also allow facile construction of isoindolinone rings that have not been easily prepared. Further studies focusing on the exploration of the carboxylic acids and anhydrides as useful coupling partners to synthesize more heterocycles is currently underway.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization of products, and copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01185.

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Notes

The authors declare no competing financial interest.

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