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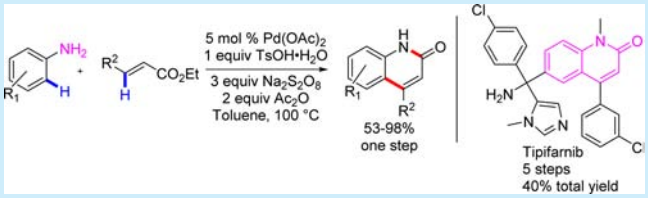
Practical Route to 2-Quinolinones via a Pd-Catalyzed C−H Bond Activation/C−C Bond Formation/Cyclization Cascade Reaction

Junliang Wu, Shaohua Xiang, Jing Zeng, Minli Leow, and Xue-Wei Liu*

Division of Chemistry and Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

Supporting Information

ABSTRACT: Quinolinone derivatives were constructed via a Pd-catalyzed C−H bond activation/C−C bond formation/cyclization cascade process with simple anilines as the substrates. This finding provides a practical procedure for the synthesis of quinolinone-containing alkaloids and drug molecules. The utility of this method was demonstrated by a formal synthesis of Tipifarnib.



Quinolinones are an important class of molecules present in a number of biologically active natural products and medicinally valuable compounds and have therefore attracted considerable attention from medicinal and synthetic organic chemists.[1] Several synthetic methodologies for the construction of such structures have been developed in the past several decades.[2] However, these procedures generally involve the use of preactivated substrates and multistep strategy and/or harsh reaction conditions which limit the functional group compatibility of these reactions.

In the past few decades, transition-metal-catalyzed functionalization of the C−H bond has emerged as a versatile strategy for chemical synthesis.[3] This synthetic strategy is intriguing for chemical and pharmaceutical industries because it may not only significantly simplify and shorten the synthetic route for various types of organic compounds but also allow the utilization of readily available, cheap and environmentally benign starting materials. Recently, there has been much progress in terms of synthesis efficiency and atom economy in highly selective functionalization of C−H bonds involving directing groups. Coordination groups such as hydroxyls,[4] carbonyls,[5] amides,[6] N-heterocycles,[7] imines,[8] pyridine *N*-oxides,[9] and carboxyls[10] are commonly used as the directing group for performing C−H bond functionalization. Although catalyzed C−H functionalization of nitrogen-containing substrates is well-known, employing anilines as substrates for C−H activation is much less common.[11] Acyls are usually introduced on the amino group to assist in the C−H bond functionalization of anilines substrates;[6a,12] therefore, the free amino group could be obtained by deacylation of acyls after the C−H bond activation process for further synthesis. The direct employment of anilines as the substrates for C−H bond activation still remains very challenging. Herein, we report our preliminary results on the synthesis quinolinone derivatives by employing simple and readily available anilines as the substrates involving C−H activation catalyzed by $Pd(OAc)_2$ via an in situ acylation and deacylation process.

We began our reaction by employing $Pd(OAc)_2$ as the catalyst and $Na_2S_2O_8$ as the oxidant. This relationship has been verified as an effective combination for catalytic functionalization of C−H bond involving a Pd(II)−Pd(0) catalyst cycle.[13] However, upon heating 5 mol % of $Pd(OAc)_2$ with aniline **1a**, ethyl acrylate **2a**, and $Na_2S_2O_8$ in toluene, no desired product **3a** was detected. Considering the difficulties associated with the formation of 4-membered ring transition state in the proposed mechanism, acetic anhydride was added as an additive to form an amide in situ. To our delight, a trace amount of **3a** was observed (entry 1). Efforts were made to optimize the reaction conditions, and a range of additives were examined. As shown in Table 1, when 2 equiv of TFA was used, **3a** was obtained in 50% yield (entry 2) while the addition of camphorsulfonic acid (CSA) gave a yield of 30% for this reaction (entry 5). Under the same reaction conditions, we were pleased to find that when *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$) was used as the additive, 83% yield of **3a** could be achieved (entry 6). On the other hand, utilization of acetic acid, benzoic acid, or an alkaline such as triethylamine as the additive could not improve the yield (entries 3 and 4). We went on to screen a number of solvents, and toluene was found to be the most effective solvent for this reaction as compared to DCE, chloroform, DMF, DMSO, and DMA (entries 10−14). It should be noted that a trace amount of product was observed when the reaction was performed at a lower temperature of 80 °C (entry 15). Hence, we concluded that 1 equiv of $TsOH·H_2O$ in toluene was the optimum condition for this catalytic C−H bond activation reaction (entry 8).

Evaluation of substituted anilines revealed that both electron-poor and -rich derivatives are effective in cyclization, and the reaction is compatible with fluoro, chloro, bromo, methyl, alkoxy, and trifluoromethyl functional groups (**3a**−**l**) as summarized in Scheme 1. The good tolerance of substrate-

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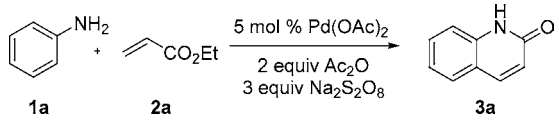
Table 1. Optimization of Reaction Conditions[a]



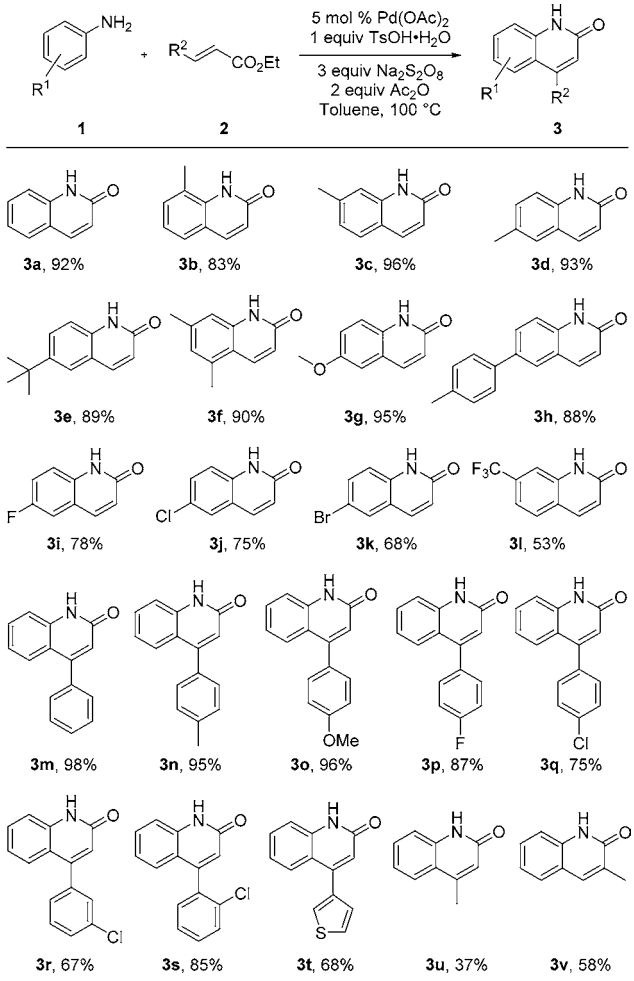
1a 2a 3a

entry	additive/loading	solvent	yield[b] (%)
1	acetic acid/2	toluene	trace
2	TFA/2	toluene	50
3	benzoic acid/2	toluene	trace
4	Et_3N/2	toluene	NR
5	CSA/2	toluene	30
6	TsOH·H_2O/2	toluene	83
7	TsOH·H_2O/3	toluene	72
8	TsOH·H_2O/1	toluene	95 (92)
9	TsOH·H_2O/0.5	toluene	67
10	TsOH·H_2O/1	DCE	72
11	TsOH·H_2O/1	CHCl3	trace
12	TsOH·H_2O/1	DMF	NR
13	TsOH·H_2O/1	DMSO	NR
14	TsOH·H_2O/1	DMA	NR
15[c]	TsOH·H_2O/1	Toluene	trace

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), $Pd(OAc)_2$ (5 mol %), $Na_2S_2O_8$ (1.5 mmol), acetic anhydride (1 mmol), additives, solvent, 2 mL, 100 °C, 36 h. [b]Yields were determined by ^1H NMR with 1,3,5-trimethoxybenzene as the internal standard; the number in parentheses refers to the yield of isolated product. [c]Reaction was conducted at 80 °C.

bearing Cl and Br provides a convenient platform for further elaboration via conventional Pd(0)-catalyzed cross-coupling (**3j**, **3k**). For *m*-toluidine and 3-trifluoromethylaniline, C−H bond activation occurred solely *para* to the methyl or trifluoromethyl group to provide the corresponding products **3c** and **3l** in 96% and 53% yields, respectively. In addition, 4-(4-methylphenyl)aniline was also a suitable substrate to provide 6-(4-methylphenyl)quinol-2-one **3h** in 88% yield. However, the reactions with anilines bearing electron-withdrawing groups, such as trifluoromethyl, nitro, or carboxyl at the *para* position, cannot give the desired quinolinone products. The substrate scope was further extended to a broad variety of substituted cinnamates. Substitutions at the *ortho*, *meta*, and *para* positions of phenyl group were all well tolerated. The results revealed that this procedure exhibited electronic dependence. The substituents on the aryl influenced the efficiency of the cyclization significantly. Electron-rich functional groups on the aryl moiety displayed higher reactivity than those with electron-deficient groups. For cinnamates substituted with electron-donating groups on the aryl moiety such as methyl and methoxy, their corresponding products **3n** and **3o** were obtained in 95% and 96% yields, respectively, while moderate to good yields of the desired products were obtained for electron-deficient cinnamates substituted with fluoro or chloro (**3p**, **3q**, **3r**, and **3s**). No desired products were observed when ethyl (2*E*)-3-(2-trifluoromethylphenyl)propenoate were employed as the substrate. In addition, heterocyclic substituents containing propenoate could also be subjected to the reaction conditions, with **3t** obtained in good yield by employing ethyl (2*E*)-3-(3-thienyl)propenoate as the substrate. It should be noted that alkyl-substituted propenoates could also be used in this reaction, and **3u** and **3v** were obtained in 37% and 58% yields by employing ethyl crotonate and ethyl methacrylate as the substrates, respectively. The reactions are not limited to the small scale described above (0.5 mmol). Quilolinone **3a** was successfully prepared on a 5 mmol scale in 80% yield, which is lower than that on a small scale (92%).

Scheme 1. Palladium-Catalyzed Direct Ring Construction of Anilines 1 with Acrylates 2[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2** (2.5 mmol), $Pd(OAc)_2$ (5 mol %), $Na_2S_2O_8$ (1.5 mmol), acetic anhydride (1 mmol), TsOH·H_2O (0.5 mmol), toluene, 2 mL, 100 °C, 36 h. [b]Isolated yields.

A plausible mechanism for this direct ring construction of anilines with acrylates is shown in Scheme 2. First, aryl-Pd complex **II** is formed via C−H activation at the 2-position carbon atom of the substrate assisted by an in situ formed acetyl on N atom. Next, Heck-type coupling of **II** with acrylate through Pd complex **III** forms intermediate **IV** and releases the Pd(0) species. This was followed by oxidation of Pd(0) by $Na_2S_2O_8$ to Pd(II) to complete the metal catalytic cycle. Under acidic conditions, the intermediate **IV** could be transferred to intermediate **V** and followed the ammonolysis of the ester with the amide to give the intermediate **VI**. Lastly, the quinolinone product was afforded by hydrolysis of intermediate **VI**. In order to get evidence for our proposed mechanism, a control reaction was carried out with intermediate **IV** in the presence of 1 equiv of TsOH·H_2O at 100 °C for 36 h. Gratifyingly, the desired product could be obtained quantitatively.

Tipifarnib (Figure 1) is a potent, orally active inhibitor of farnesyl protein transferase which has been found to exhibit potent activity against neoplastic diseases, antineoplastic activity in solid tumors, such as breast cancer, as well as in

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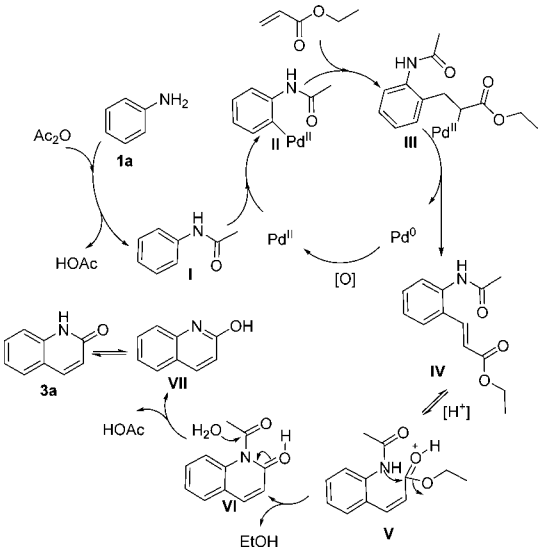
Scheme 2. Plausible Mechanism for the Cyclization Reaction



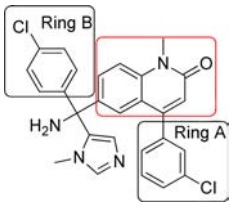
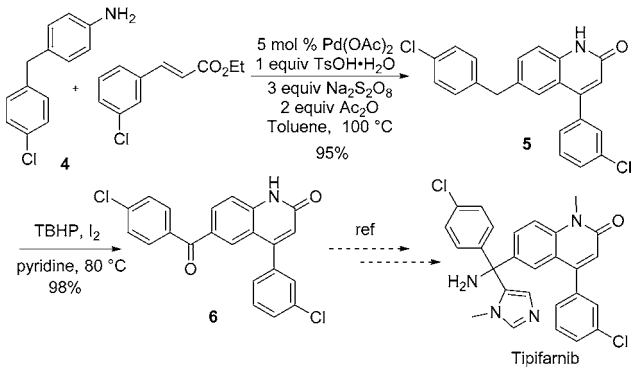


Figure 1. Tipifarnib.

hematological malignancies, found in leukemia.The key feature of Tipifarnib is the quinolinone-containing ring A and ring B at the 4 and 6 positions, respectively. To date, several strategies for the synthesis of Tipifarnib have been developed.[14] However, these procedures generally involved multisteps construction of quinolonine core and sequentially introduction of ring A and ring B on quinolinone, which resulted in more chemical waste and overall low total yield.

As a utility of our method, we provide a concise route for the formal synthesis of Tipifarnib, as shown in Scheme 3. We first tried to utilize 4-amino-4′-chlorobenzophenone as the starting material for the Tipifarnib synthesis. However, no desired product was detected from the reaction mixture, and this indicates that the C−H bond activation was obstructed by the lower electron density of the substrate. To our delight, when 4-amino-4′-chlorodiphenylmethane **4** was used as the starting material, quinolinone **5** was generated in 95% yield. Treatment of intermediate **5** with *tert*-butyl hydroperoxide in the presence of a catalytic amount of pyridine and iodine afforded quinolinone **6** in 98% yield, which can be subsequently converted to Tipifarnib in three steps according to reported literatures.[14b,15]

Scheme 3. Synthesis of Tipifarnib



In summary, we have developed a concise and general strategy for the construction of quinolinone by a one-pot Pd-catalyzed cascade C−H bond activation reaction. This strategy includes ammonolysis, C−H bond activation, and a cyclization reaction successively in one pot. A broad range of quinolinone derivatives have been prepared in good to excellent yields. The utility of this method was demonstrated by a formal synthesis of Tipifarnib.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xuewei@ntu.edu.sg.

Notes

The authors declare no competing financial interest.

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