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Preparation of 2-aryl derivatives of tanshinone I through a palladium-catalyzed C_{sp2}–H activation/arylation approach

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A facile and efficient synthetic approach under the catalyst system of $Pd(OAc)_2$/KOAc/TBAB/DMF was developed allowing for rapid preparation of 2-arylation derivatives of the natural product tanshinone I. This approach was featured by palladium-catalyzed C–C coupling through direct C_{sp2}–H activation at the α-position of the furan ring of tanshinone I. Compared to the literature procedures, our protocol exhibited better atom-economy and much improved yields.

Salvia miltiorrhizae Bunge (Danshen in Chinese), one of the most famous Chinese traditional medicines (TCMs), has been used extensively for treatment of cardiovascular and cerebrovascular diseases, neurodegenerative diseases as well as inflammatory diseases for thousands of years in Asian countries.[1] Tanshinone I (**1**), isolated from the roots of the herb,[2] is one of the most abundant bioactive components. This naturally occurring abietane-type norditerpenoid quinone was reported to have diverse pharmacological properties,[3–6] including anticancer activities[7] (Fig. 1). Unfortunately, further clinical development of tanshinone I for cancer therapy has been limited by its relatively moderate potency, poor aqueous solubility, short half-life, and low bioavailability.[8] Consequently, structural modifications on the tetracyclic furoquinone scaffold of tanshinone I have become an attractive strategy to achieve more potent analogues with better drug-like properties.

Recently, we have obtained some tanshinone I derivatives with variant substitutions on ring A through a total synthesis approach.[9] The majority of other medicinal chemistry efforts was mostly focused on modification of the α-position of furan ring due to its relative high reactivity.[10] Amongst these, Rong et al. recently synthesized and patented a series of 2-aryl substituted tanshinone I derivatives through a two-step reaction process, including bromination of tanshinone I followed by Suzuki coupling with boric acid or borate. Some of these derivatives displayed significantly improved antitumor activities compared to tanshinone I (Fig. 1).[10c] Nevertheless, as shown in Figure 2, for most of the derivatives, the overall yields of this two-step process were low (around 20%) due to the low efficiency in the Suzuki coupling, which hampered further SAR studies and pharmacological evaluations of these compounds. Therefore, more facile and efficient synthetic approaches to readily access 2-aryl derivatives are still needed.

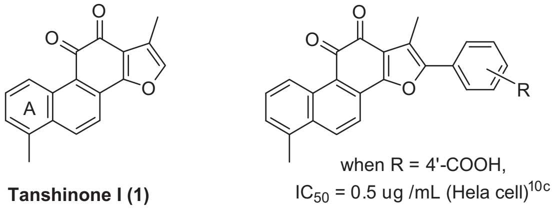

Figure 1. Tanshinone I and its 2-aryl analogues.

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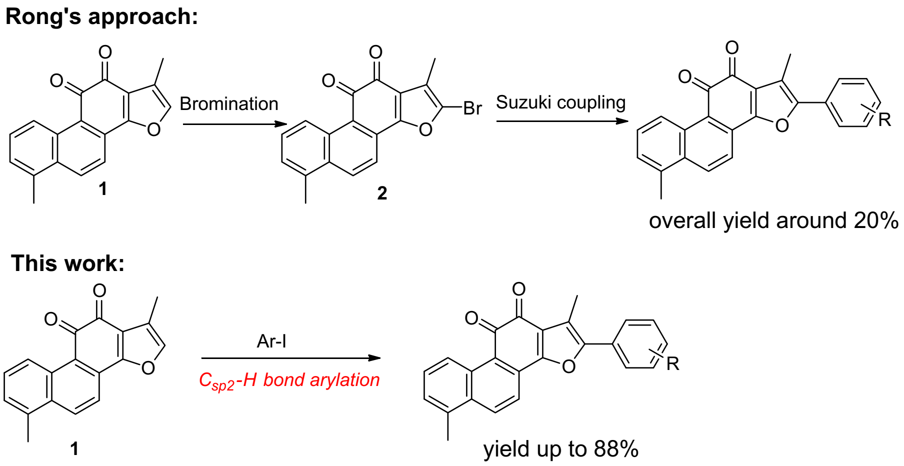
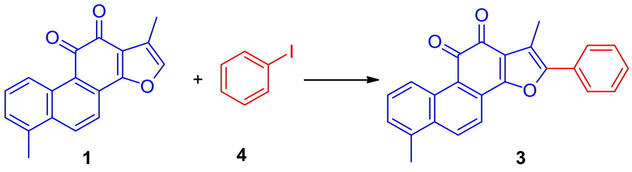


Figure 2. Approaches to 2-aryl analogues of tanshinone I.

Table 1
Reaction optimization for the synthesis of **3**[a]



Entry	Catalyst (**a**)	Base (**b**)	Ratio (**1**/**4**/**a**/**b**)	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	Cs_2CO_3	1.0/2.0/0.05/3.0	DMF	23
2	$Pd(OAc)_2$	$NaHCO_3$	1.0/2.0/0.05/3.0	DMF	34
3	$Pd(OAc)_2$	KOAc	1.0/2.0/0.05/3.0	DMF	74
4	$Pd(OAc)_2$	K_2CO_3	1.0/2.0/0.05/3.0	DMF	70
5	$Pd(OAc)_2$	KOAc	1.0/3.5/0.1/5.0	DMF	77
6[c]	$Pd(OAc)_2$	KOAc	1.0/3.5/0.1/5.0	DMF	88
7[c]	$Pd(OAc)_2$	KOAc	1.0/3.5/0.1/5.0	Dioxane	58
8[c]	$Pd(OAc)_2$	KOAc	1.0/3.5/0.1/5.0	Toluene	43
9[c]	$PdCl_2$	KOAc	1.0/3.5/0.1/5.0	DMF	71
10[c]	$Pd(PPh_3)_4$	KOAc	1.0/3.5/0.1/5.0	DMF	78

[a] Reaction conditions: **1** (0.1 mmol), **4**, catalyst, base and additive were dissolved in the solvent (2 mL) in a sealed tube, N_2, 100 °C, 3 h.
[b] Isolated yield.
[c] 2.0 equiv TBAB was used as the additive.

Recently, transition metal-catalyzed C–C coupling[11] through direct C_{sp2}–H activation for aryl functionalization of furans has been extensively studied.[12] Inspired by these advances, we envisioned that this direct arylation methodology could be utilized to create aryl–aryl bond at the α-position of furan ring of tanshinone I as well (Fig. 2). Herein, we report on a facile and efficient synthesis of 2-aryl derivatives of tanshinone I through a palladium-catalyzed C_{sp2}–H activation/arylation.

Initially, tanshinone I (**1**) was directly employed as a model substrate to react with iodobenzene under the condition of $Pd(OAc)_2$ and Cs_2CO_3 in DMF.[13] As expected, 2-phenyl derivative **3** was obtained as the only isolated product though in much low yield (23%) (entry 1, Table 1). We then set to optimize the reaction condition to achieve better yields. To this end, a series of bases, palladium catalysts, solvents, and other reaction parameters were screened, and the results are summarized in Table 1. It was found that the base had a significant impact on the yield, and KOAc proved to be the best thus leading to the product in 74% yield (entry 3). Slight improvement was observed when the molar ratio was changed to 1.0/3.5/0.1/5.0 (entry 5). To our delight, the yield was increased to 88% when tetrabutylammonium bromide (TBAB) was added (entry 6). Replacement of either palladium catalyst or the solvent led to lower yields (entries 7–10).

With the optimized reaction conditions[14], we then continued to explore the substrate scope and limitation. The arylation scope with respect to aryl halides was is presented in Scheme 1. Arylation of **1** with 1-iodo-4-methylbenzene and 1-iodo-4-methoxybenzene afforded the desired *para*-substituted products **5** and **6** in 84% and 75% yields, respectively. The *meta*-substituted products **8** and **10** were also achieved in 83% yields when 1-

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