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Palladium(II)-Catalyzed C−H Bond Activation/C−C Coupling/Intramolecular Tsuji−Trost Reaction Cascade: Facile Access to 2*H*-Pyranonaphthoquinones

Jinlei Bian,[†] Xue Qian,[†] Nan Wang,[†] Tong Mu,[†] Xiang Li,[†] Haopeng Sun,[†] Lianshan Zhang,[‡] Qidong You,*[,†,§] and Xiaojin Zhang*[,†,∥]

[†]Jiangsu Key Laboratory of Drug Design and Optimization, China Pharmaceutical University, Nanjing 210009, China

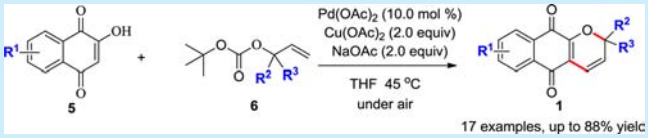
[‡]National Engineering and Research Center for Target Drugs, Lianyungang, 222000, China

[§]State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China

[∥]Department of Organic Chemistry, School of Science, China Pharmaceutical University, Nanjing 210009, China

Supporting Information

ABSTRACT: An efficient one-pot synthesis of 2*H*-pyranonaphthoquinone was achieved via a palladium-catalyzed C−H bond activation/C−C bond formation/intramolecular Tsuji−Trost reaction cascade. The unprecedented procedure exhibits excellent functional group tolerance, giving the target naphthoquinones in moderate to good isolated yields (40−88%) under mild reaction conditions. Scalable production of the product can make this reaction a method of choice for the synthesis of 2*H*-pyranonaphthoquinones.



2*H*-Pyranonaphthoquinone is a special class of quinone-containing compounds with important biological activities, including anti-inflammatory, antitumor, and antimicrobial activity.[1] Many compounds of this class are found in natural products such as α-xiloidone (**1a**), 7-methyldehydro-α-lapachone (**2**), α-caryopterone (**3**), and pyranokunthone B (**4**) (Figure 1).[2] In general, these 2*H*-pyranonaphthoquinones

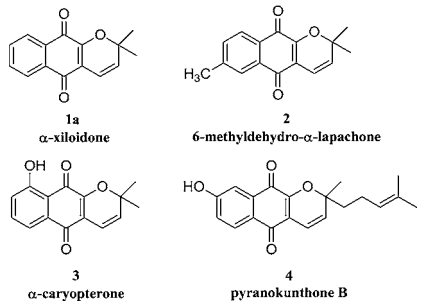


Figure 1. Examples of natural 2*H*-pyranonaphthoquinones.

are obtained in small quantities from plant extracts.[3] Therefore, much effort has been devoted to their synthesis, and considerable advances have been developed over the past several decades.[4] However, the present methods for the synthesis of these compounds are very limited, and in view of minimizing the waste/side product formation in 2*H*-pyranonaphthoquinone synthesis, the search for an additional efficient synthesis protocol is necessary.

During the past several decades, palladium-catalyzed functionalization of C−H activation/C−C bond formation has emerged as a powerful tool for chemical synthesis.[5] This synthetic strategy is attractive from the viewpoint of synthetic simplicity and step economy. Much progress has been achieved in terms of synthesis efficiency and atom economy in the highly selective functionalization of C−H bonds involving directing substituents.[6,7] In addition, Pd-catalyzed Tsuji−Trost allylic substitution reactions are widely employed for constructing C−O, C−C, C−N, and C−S bonds.[8] Recently, the notion of combining several metal-mediated processes in relay-type domino sequences has drawn particular attention.[9] Therefore, in this context, we were attracted to developing a tandem palladium-catalyzed synthesis of 2*H*-pyranonaphthoquinones through a C−H/C−H coupling and sequential intramolecular C−O bond formation with an exceptionally mild protocol.

We initially investigated the reaction conditions for 2-hydroxy-1,4-naphthoquinone (**5a**) and *tert*-butyl-(2-methylbut-3-en-2-yl) carbonate (**6a**) as model substrates. When **5a** was treated with **6a** in the presence of $Pd(OAc)_2$, the oxidant $Cu(OAc)_2$, and the base NaOAc in DMF at room temperature for 3 h, the desired natural product **1a** was gratifyingly obtained in 43% yield (Table 1, entry 1). The effect of temperature was first optimized, and the yield was substantially increased by raising the temperature to 45 °C (entries 2−3). We then turned toward examining the effect of solvent, and THF was found to be the best one for this reaction among the tested solvents (entries 4−8). When the model reaction was performed in the presence of $Pd(OAc)_2$ (10.0 mol %), THF as solvent at 45 °C

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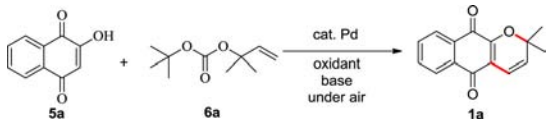
Table 1. Reaction Optimization[a]



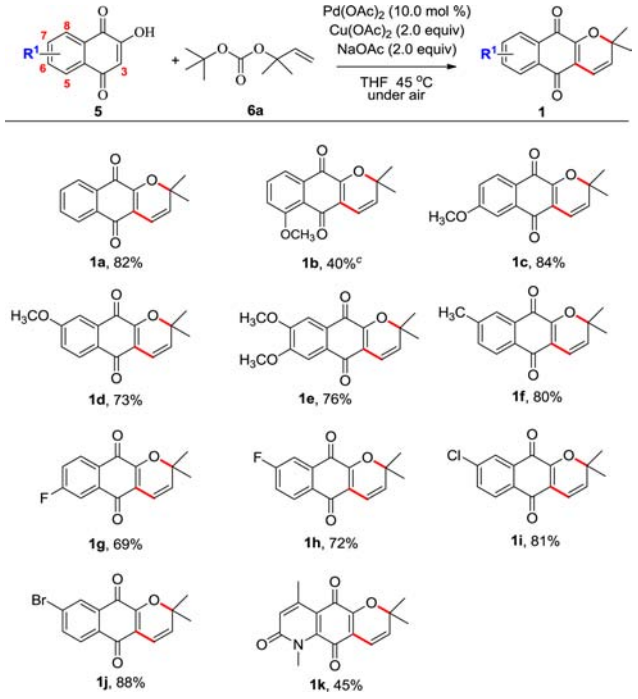
entry	cat.	oxidant	solvent	temp (°C)	yield[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	25	43
2	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	35	48
3	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	45	55
4	$Pd(OAc)_2$	$Cu(OAc)_2$	dioxane	45	44
5	$Pd(OAc)_2$	$Cu(OAc)_2$	dioxane/H_2O	45	35
6	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	45	trace
7	$Pd(OAc)_2$	$Cu(OAc)_2$	THF	45	82
8	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	45	60
9	$Pd(OAc)_2$	$Na_2S_2O_8$	THF	45	32
10	$Pd(OAc)_2$	AgOAc	THF	45	trace
11	$Pd(OAc)_2$	BQ	THF	45	NR
12	$Pd(OAc)_2$	$AgNO_3$	THF	45	20
13	$Pd(OAc)_2$	$Cu(OAc)_2$	THF	45	45[c]
14	$PdCl_2$	$Cu(OAc)_2$	THF	45	trace
15	$Pd(TFA)_2$	$Cu(OAc)_2$	THF	45	trace
16	$Pd(dba)_2$	$Cu(OAc)_2$	THF	45	trace
17	$Pd(OAc)_2$ (5.0 mol %)	$Cu(OAc)_2$	THF	45	70[d]

[a]Reaction conditions: **5a** (0.50 mmol), **6a** (2.5 mmol, 5.0 equiv), Pd catalyst (10.0 mol %), oxidant (2.0 equiv), and base (2.0 equiv) in solvent (15 mL) for 3 h under air. [b]Isolated yield. [c]Under nitrogen. [d]10 h. NR = No reaction.

for 3 h, $Cu(OAc)_2$ is the most effective common oxidant among $Na_2S_2O_8$, AgOAc, BQ (1,4-benzoquinone), and $AgNO_3$ (entries 9−12). Conducting the reaction under a nitrogen atmosphere (balloon) decreased the isolated yield sharply to 45% (entry 13). In addition, when $Pd(OAc)_2$ was replaced by $PdCl_2$, $Pd(TFA)_2$, and $Pd(dba)_2$, poor results were observed (entries 14−16). Lowering the catalyst loading from 10.0 to 5.0 mol % was unfavorable, and no reaction was observed in the absence of the catalyst (entry 17). Therefore, we concluded that the optimized reaction conditions consist of $Pd(OAc)_2$ (10.0 mol %), $Cu(OAc)_2$ (2 equiv), NaOAc (2 equiv), and THF (solvent) at 45 °C for 3 h under air.

With the optimized reaction conditions in hand, other naphthoquinones were systematically screened. As shown in Scheme 1, a relatively broad range of naphthoquinone derivatives with substituents at the C5, C6, or C7 position of the naphthoquinone ring were successfully transformed to desired products in moderate to good yields. The electronic nature has a slight influence on the reaction outcome. For example, the electron-rich groups such as $-CH_3$ and $-OCH_3$ substituted naphthoquinones were tolerated in this transformation, providing the desired products **1b**−**1f** in 40−84% yields. Of particular note, 5-methoxy naphthoquinone showed inferior reactivity compared to the corresponding 6- or 7-methoxy naphthoquinone, and a higher temperature (60 °C) was required. In addition, the electron-withdrawing substituted naphthoquinones also showed good reactivity and gave good yields. To our interest, the nitrogen-containing heteroaromatic substrate also gave the cyclization product **1k** in 45% yield. This compound could be regarded as the merged molecule for two natural products α-xiloidone and deoxynyboquinone

Scheme 1. Substrate Scope of Naphthoquinones[a,b]

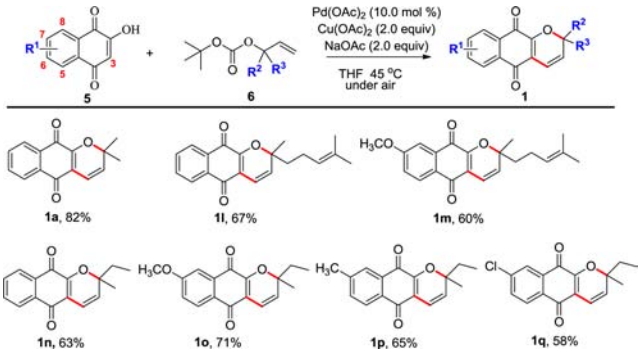


[a]Reaction conditions: **5** (0.50 mmol), **6a** (2.5 mmol, 5.0 equiv), $Pd(OAc)_2$ (10.0 mol %), $Cu(OAc)_2$ (2.0 equiv), and NaOAc (2.0 equiv) in THF (15 mL) for 3 h under air. [b]Isolated yield. [c]The reaction was carried out at 60 °C.

(DNQ),[10,11] which were supposed to be effective anticancer drugs (Figure S2).

To further expand the substrate scope, we next turned our attention toward testing the feasibility of the replacement of **6a** (Scheme 2). Different olefinic alcohol derivatives reacted well

Scheme 2. Substrate Scope of Olefinic Alcohol Derivatives[a,b]



[a]Reaction conditions: **5** (0.50 mmol), **6** (2.5 mmol, 5.0 equiv), $Pd(OAc)_2$ (10.0 mol %), $Cu(OAc)_2$ (2.0 equiv), and NaOAc (2.0 equiv) in THF (15 mL) for 3 h under air. [b]Isolated yield.

with naphthoquinones and generated the corresponding products in 58−82% yields (**1a**, **1l**−**q**). As shown in Scheme 2, the $Pd(OAc)_2$ catalyst allowed the coupling of **6c** with naphthoquinones bearing electron-donating, electron-neutral, and electron-withdrawing groups at the naphthoquinone ring to produce **1n**−**q** in 58−71% yields. To demonstrate the practicability of the method, the model procedure was successfully scaled up with comparable yield. The natural

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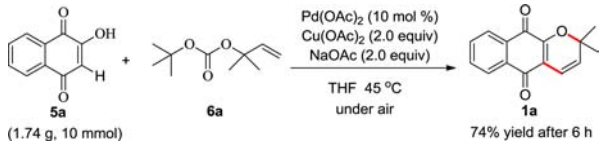
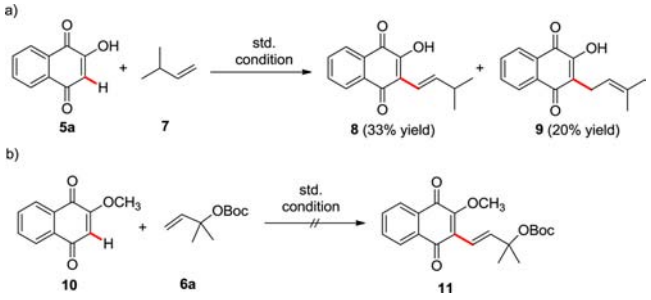
product **1a** (1.78 g, 74%) was prepared when the reaction was run in 10 mmol scale (Scheme 3).

Scheme 3. Scale-up Experiment



To gain insight into the reaction mechanism, we conducted some additional control experiments (Scheme 4). When

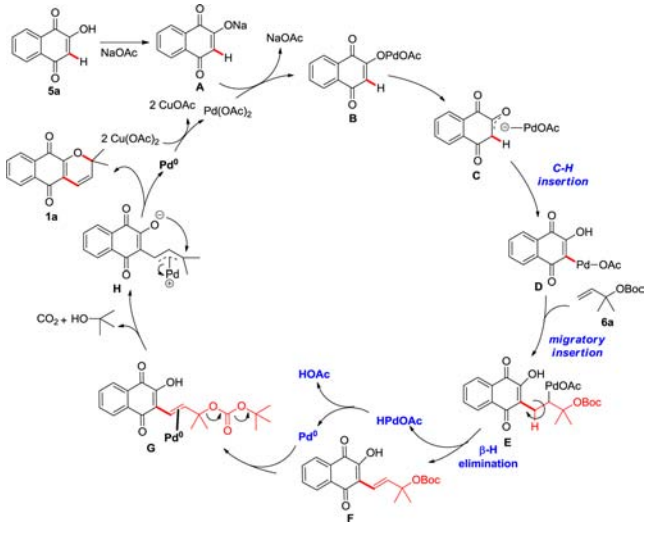
Scheme 4. Control Experiments



substrate **5a** and 5 equiv of 3-methyl-1-butene (**7**) were subjected to the standard conditions, the reaction was found to be stagnated at the stage of C−H/C−H coupling to produce the products **8** and **9** (Scheme 4a). In addition, when the hydroxyl group in the model substrate (**5a**) was protected with methyl group, the reaction would fail to conduct a C−H/C−H coupling reaction (Scheme 4b). From all these control experiments it is speculated that the reaction proceeds through a C−H bond activation/C−C bond formation/intramolecular Tsuji−Trost reaction cascade in the presence of the hydroxyl group.

A possible catalytic cycle for these reactions, employing model substrates **5a** and **6a** for illustrative purposes, is shown in Scheme 5 based on these experiments. The first step is the formation of the complex **A** as a sodium salt. Exchange between

Scheme 5. Possible Mechanism for Reactions



the alkoxide and the palladium acetate gives the complex **B**, which then formed the anionic species **C**. Next, Pd(II) catalyzed the C−H bond activation at the 3-position carbon atom of **C** assisted by the hydroxyl group to afford a C3-palladated species **D**, which was further followed by the migratory alkene insertion to form species **E**. Subsequently, the obtained **E** underwent β-H elimination to afford the product **F** and Pd(0) species. The Pd(0) can catalyze the formation of the π-allylpalladium complex as a cationic species with inversion of configuration, leading to the formation of the alkoxide.[12] Meanwhile, the removal of the Boc protecting group would be conducted simultaneously in the presence of Pd(0), forming the intermediate **H**. Then, the nucleophile alkoxide attacked the backside of the coordinated π-allyl giving the target compound **1a** and Pd(0) catalyst, which is reoxidized by 2 equiv of $Cu(OAc)_2$ to regenerate the Pd(II) catalyst to complete the catalytic cycle. The mechanism provided a rational explanation for the generation of compounds **8** and **9** in the control experiment (Scheme 4a).

In conclusion, we have developed a simple, mild, and scalable strategy for the preparation of 2*H*-pyranonaphthoquinones through a one-pot Pd-catalyzed reaction. This transformation includes C−H insertion, C−C bond formation, and an intramolecular Tsuji−Trost reaction successively in one pot. Scalable production of the product can make this reaction a method of choice for the synthesis of 2*H*-pyranonaphthoquinones. Further investigations into the mechanism and applications of this reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01304.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zxj@cpu.edu.cn.
*E-mail: youqd@163.com.

Notes

The authors declare no competing financial interest.

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