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Naphtho[2,3-b]furan-4,9-dione synthesis via palladium-catalyzed reverse hydrogenolysis

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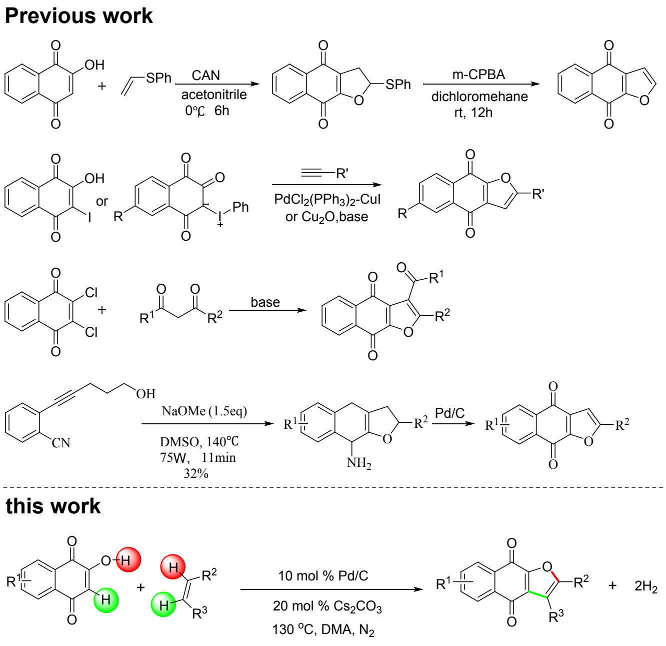
A reverse hydrogenolysis process has been developed for two-site coupling of 2-hydroxy-1,4- naphthoquinones with olefins to produce naphtha[2,3-b]furan4,9-diones and hydrogen(H_2). The reaction proceeds catalyzed by commercially available Pd/C without oxidants and hydrogen acceptors, thereby providing an intrinsically waste-free approach for the synthesis of functionalized and potentially biologically relevant naphtha[2,3-b]furan-4,9-diones.

The C–H bonds and X (N, O, S, and P)–H bonds are the most commonly encountered structural motifs in organic molecules. Consequently, the development of selective, direct and efficient methods for converting C–H and X–H bonds into C–X bonds may greatly simplify the synthesis of complex organic molecules and represent an attractive long-standing goal in chemistry. However, the conversion of C–H and X–H bonds into the C–X bonds is extremely difficult to achieve so that only a few catalytic systems have been developed for this conversion by resorting to stoichiometric hydrogen acceptors or oxidants. These hydrogen acceptors or oxidants are often expensive or highly hazardous or toxic compounds, and may generate a large amount of environmental effluents in industrial production.[1] The use of stoichiometric expensive metallic or highly toxic oxidants or hydrogen acceptors is problematic in industrial settings, which limits the applications of the reactions in large-scale synthesis. In this context, there is a great need for development of an atom- and step-efficient, and intrinsically waste-free catalytic system available for performing the conversion. The catalytic reverse hydrogenolysis, the reverse process of hydrogen cracking, can convert C–H bonds and X–H bonds into the C-X bonds with the evolution of hydrogen without the need for a stoichiometric oxidant or a hydrogen acceptor, and thereby have the potential to reshape retrosynthetic analysis strategies, and can streamline the synthesis of natural products, medicines and materials. Adding to the advantages, reverse hydrogenolysis processes are able to harness native structural units (C–H and X–H bonds) of starting material to construct chemical bonds, thereby dispensing with the need for substrate prefunctionalization. However, despite the advantages and potentials, synthetic methods utilizing reverse hydrogenolysis procedures remain extremely rare to date.



Scheme 1 Methods for synthesis of 2-furanonaphthoquinones.

Herein we reported our results toward achieving this goal. In the exploration of rapid and green methods for preparation of naphtho[2,3-b]furan-4,9-dione, we developed a catalytic reverse hydrogenolysis reaction where 2-hydroxy-1,4-naphthoquinones were directly coupled with a variety of olefins to produce a wide range of naphtha[2,3-b]furan4,9-diones and H_2 without oxidants and hydrogen acceptors. The palladium-catalyzed reverse hydrogenolysis reaction features

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the starting material skeleton structures being almost completely preserved into the products, with only two hydrogen atoms missing.

Naphtho[2,3-b]furan-4,9-diones constitute an important class of structural units commonly present in natural products, pharmaceutically active compounds, and other functional synthetics. Many naphtho[2,3-b]furan-4,9-diones are found to have a broad spectrum of biological activities such as antimicrobial, antifungal, antiviral, radical scavenging, antiplatelet and trypanocidal activities;[2] in particular, antitumor activity.[3] The selection of naphtho[2,3-b]furan-4,9-diones synthesis for this study was primarily inspired by the discovery of the antitumor activity of 2-acetylated naphtho[2,3-b]furan-4,9-dione.[4] This naphtho[2,3-b]furan-4,9-dione core containing compound, which was first isolated from Tabebuia cassinoides, is capable of killing many different types of cancer cells, without causing damage to normal cells under certain exposure conditions.[5] Because of the importance of naphtho[2,3-b]furan-4,9-dione skeleton toward therapeutic development and the search for clinically superior analogs, several synthetic methods have been developed to construct naphtho[2,3-b]furan-4,9-dione structural ring systems. Despite their many attractive features; however, these synthetic methods suffer from several limitations, including (i) the need for stoichiometric strong oxidants (e.g., ceric ammonium nitrate) and lead to equimolar amounts of byproducts;[6] (ii) inefficiencies associated with the need for substrate prefunctionalization and long routes of synthesis;[7] and (iii) harsh reaction conditions or use of expensive or highly toxic reagents or the starting materials not readily available.[8]

The development of an innovative approach capable of overcoming these problems for synthesis of naphtho[2,3-b]furan-4,9-diones is therefore highly desirable. In light of retrosynthetic analysis, we imagine a hydrogenolysis process whereby naphtho[2,3-b]furan-4,9-diones are cleaved into olefins and 2-hydroxy-1,4-naphthoquinones, two readily available fragments, by hydrogen. Catalytic coupling of these two fragments produce naphtho[2,3-b]furan-4,9-diones with hydrogen release via a reverse hydrogenolysis process, which would be a very attractive synthetic strategy of naphtho[2,3-b]furan-4,9-diones. Recently, we reported a class of palladium(0)-catalysed oxidant- and acceptor-free dehydrogenation reactions accompanied by the release of hydrogen, in which intramolecular C-H and X-H bonds are converted to C–X bonds, and alkanes are converted to the alkenes.[9] These reactions manifest as a acceptorless dehydrogenation process or a reverse process of hydrogenolysis. Encouraged by these results and guided by the concept of reverse hydrogenolysis, we formulated direct coupling of 2-hydroxy-1,4-naphthoquinones and olefins to produce naphtho[2,3-b]furan-4,9-diones and hydrogen(H_2), aiming at further exploring and developing intermolecular reverse hydrogenolysis synthetic methodologies. However, this synthetic method designed requires selective scission of three C(sp^2)–H bonds and a O–H bond and metatheses of them into a C(sp^2)–C(sp^2) bond, a C(sp^2)–O bond, and two H–H bonds without use of a stoichiometric oxidant or a hydrogen acceptor, which represents an intriguing but formidable challenge.

Table 1 Reaction optimization for the synthesis of naphtho[2,3-b]furan-4,9-diones.[a]

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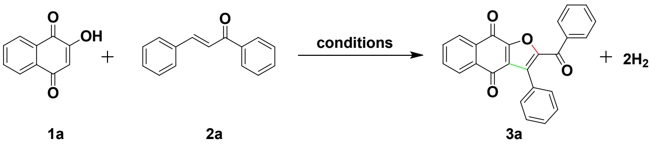

Entry	1a:2a [equiv]	Conditions	Yield [b] [%]
1	1:2	1ml DMA/ 10 mol% Pd/ 50 mol% Cs_2CO_3/120℃/ N_2	70
2	1:2	1ml DMF/ 10 mol% Pd/ 50 mol% Cs_2CO_3/ 120℃/ N_2	47
3	1:2	1ml DMSO/ 10 mol% Pd/ 50 mol% Cs_2CO_3/ 120℃/ N_2	45
4	1:2	1ml DMA/ 10 mol% Pd/ 50 mol% TsOH/ 120℃/ N_2	0
5	1:2	1ml DMA/ 10 mol% Pd/ 120℃/ N_2	10
6	1:2	1ml DMA/ 10 mol% Pd/ 50 mol% K_2CO_3/ 120℃/ N_2	69
7	1:2	1ml DMA/ 10 mol% Pd/ 50 mol% NaOH/ 120℃/ N_2	0
8	1:2	1ml DMA/ 10 mol% Pd/ 10 mol% Cs_2CO_3/ 120℃/ N_2	63
9	1:2	1ml DMA/ 10 mol% Pd/ 20 mol% Cs_2CO_3/ 120℃/ N_2	83
10	1:2	1ml DMA/ 10 mol% Pd/ 20 mol% Cs_2CO_3/ 110℃/ N_2	63
11	**1:2**	**1ml DMA/ 10 mol% Pd/ 20 mol% Cs_2CO_3/ 130℃/ N_2**	**84**
12	1:2	1ml DMA/ 0 mol% Pd/ 20 mol% Cs_2CO_3/ 130℃/ N_2	0
13	1:2	1ml DMA/ 10 mol% Pd/ 20 mol% Cs_2CO_3/ 130℃/ O_2	57
14	1:1	1ml DMA/ 10 mol% Pd/ 20 mol% Cs_2CO_3/ 130℃/ N_2	67
15	2:1	1ml DMA/ 10 mol% Pd/ 20 mol% Cs_2CO_3/ 130℃/ N_2	80

[a] Reaction condition:0.2mmol substrates, solvent, Pd/C, [b] Isolated yields

To explore the feasibility of this two-site reverse hydrogenolysis reaction, 2-hydroxy-1,4-naphthoquinone and a chalcone were first selected as the representative substrates and Pd/C as the catalyst. Because catalysts are known to can promote both the forward and reverse reactions simultaneously, we speculated that Pd/C, a widely accepted hydrogenation or hydrogenolysis catalyst, can also be used to catalyze reverse hydrogenolysis. The initial experiment was performed with 10 mol % of Pd, 1 mL of DMA, 50 mol% Cs_2CO_3, 120°C, N_2 atmosphere, and reaction for 30 hour, the reaction provided us with an exciting result of 70% isolated yields, which clearly indicated the assumption of synthesis of naphtho[2,3-b]furan-4,9-diones via reverse hydrogenolysis is feasible. A systematic study was undertaken to optimize the reaction conditions, including reaction temperature, solvent, base, and use amount of the catalyst and the results are partially exhibited in Table 1 (total results see electronic supplementary information). As can be seen, strong polar aprotic solvents are beneficial to the reaction. The effects of various acidic and basic additives on the reaction was evaluated. Although most acidic and basic additives screened were unable to promote the desired reaction, alkali carbonates were found effective on the reaction, Cs_2CO_3 is among the best of alkali carbonates. However, overuse of Cs_2CO_3 can lead to selectivity decrease. The reaction offered high selectivity but relatively low conversion in the absence of both acids and bases. It was worth noting that molecular oxygen did not provide expected high isolated yields. In fact, despite high conversion, molecular oxygen dramatically reduces the selectivity of the reaction, which arises maybe because the reaction is inherently prone to side-reactions under oxidative conditions. To our delight, we obtained 84%

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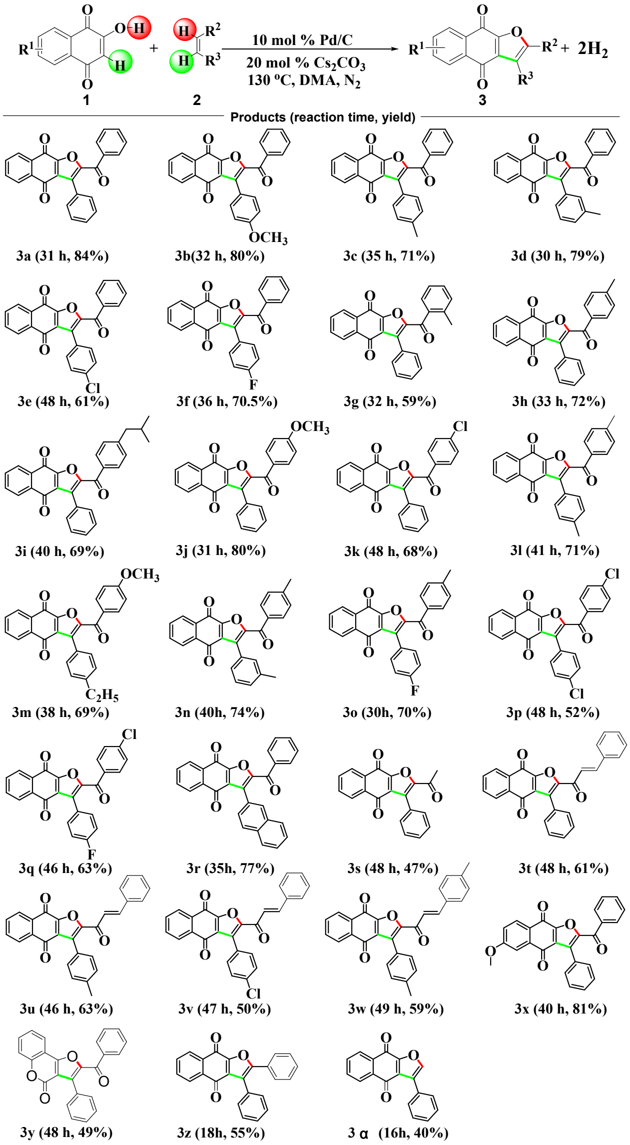
Table 2 Synthesis of naphtho[2,3-b]furan-4,9-diones catalyzed by Pd/C [a, b]



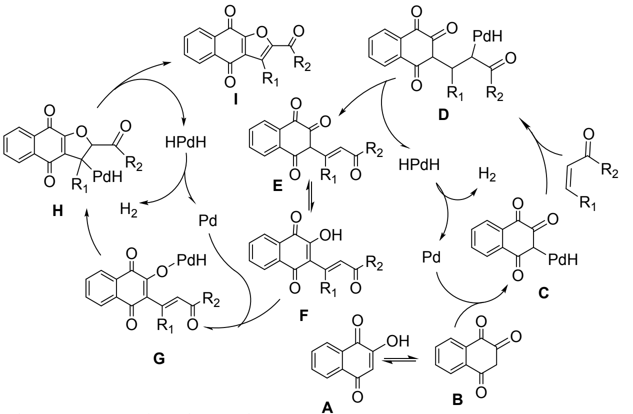
[a] Reaction conditions: 0.2 mmol substrates, 10 mol% Pd/C (10%), 20 mol% Cs_2CO_3, 1ml DMA, 130 °C, N_2 atmosphere, the mole ratio of substrate 1: substrate 2 is 1:2.

[b] Isolated yields.

isolated yield with the optimized reaction conditions of 10 mol% Pd, 20 mol% Cs_2CO_3, 1atm of N_2, and 130 °C.

After having established the optimized conditions, we proceeded to investigate the scope of 2-hydroxy-1,4-naphthoquinones and olefins for this reverse hydrogenolysis process. The results showed that this synthetic method was suitable for large numbers of substituted α, β-unsaturated enones. As shown in table 2, the enones with a variety of groups such as methyl, ethyl, isobutyl, methoxyl could be directly coupled with 2-hydroxy-1,4-naphthoquinone to give moderate to high isolated yields. Fluorine- and chlorine-containing enones were unaffected. Non-aromatic enones such as 4-phenyl-3-buten-2-one (2s) and substituted 1,5-diphenylpenta-1,4-dien-3-ones (2t, 2u, 2v, 2w) could also be smoothly coupled with the 2-hydroxy-1,4-naphthoquinones to afford the corresponding naphtho[2,3-b]furan-4,9-diones with moderate isolated yields.[10] To further explore the substrate range of olefins, we carried out the reaction using non-Michael acceptor olefins, e.g., styrene and stilbene as the partners of 2-hydroxy-1,4-naphthoquinones. To our delight, the reverse hydrogenolysis reaction could also provide the corresponding products (Table 2, 3z, 3α). The result clearly showed that the substrate scope of olefins was not limited to Michael acceptor olefins. For 2-hydroxy-1,4-naphthoquinone substrates, the naphthoquinones bearing functional groups seldom interfered with the reverse hydrogenolysis reaction. For example, the reaction obtained 81% isolated yields when substrate 2x was coupled with chalcone under the optimized coupling conditions. Furthermore, 2-hydroxy-1,4-naphthoquinones could be replaced with 3-hydroxy-4H-chromen-4-ones. When the later was used as the coupling partner of a chalcone, the reverse hydrogenolysis reaction could provide 49% yields of the corresponding product (3y). The result clearly indicated that the coupling partners of chalcone were not limited to naphthoquinones; a range of 3-hydroxy-4H-chromen-4-ones would be viable in the reverse hydrogenolysis reaction.

Subsequently, we undertook preliminary mechanistic studies to manage to have an insight into the formation of the C-C and the C-O bonds. Because α, β-unsaturated enones are a class of typical Michael acceptors, we originally thought that the C-C bond formation involved a Michael addition. However, the hypothesis that the C-C bond is formed through a Michael addition is questioned by a disproof. As can be seen in Table 2, the reverse hydrogenolysis reaction could also occur when α, β-unsaturated enones were replaced by non-Michael acceptor olefins. For example, 2-hydroxy-1,4-naphthoquinone could be coupled with styrene and stilbene to produce the corresponding products (3z, 3α). The results showed that the C-C bond formation did not necessarily need to undergo a Michael addition reaction. By contrast, the C-C bond formation via a formal Heck reaction is relatively rational. The Heck reaction-like process starts with a keto–enol tautomerism equilibrium. Subsequently, the palladation of the carbonyl α-C-H bond of the intermediate B forms the organopalladium C (see scheme 2). The process of the palladium (0) inserting into the electron-poor C-H bond to form the intermediate of palladium (II) complex C is electronically matched, and similar to that of palladium (0) inserting into the C-X bonds of Heck



Scheme 2 Proposed catalytic cycle.

reactions. The C-O bond formation also underwent a formal Heck reaction process, in which involves oxidative addition, syn addition and beta-hydride elimination steps. In our previous studies, we reported similar processes of the C-O bond formation where phenolic or carboxylic acidic hydroxyl groups could be coupled with olefins to form C(sp^2)-O bonds with release of H_2.[9c, 9d, 9f] When the olefins were styrene and stilbene, the formation of C-O bonds (from F to I) is very similar to a process of C-O formation we have reported previously. [9c]

In conclusion, we have developed a general approach to the synthesis of complex naphtha[2,3-b]furan-4,9-diones via the direct palladium catalyzed reverse hydrogenolysis coupling of 2-hydroxy-1,4-naphthoquinones and a variety of olefins. The reaction does not need for oxidants and hydrogen acceptors, with H_2 as the only byproduct. The high isolated yields and atom economy, broad substrate scope, and the use of a simple and recycled catalyst of the catalytic system highlight that the reaction is intrinsically easy to industrializate. This reverse hydrogenolysis process also provides a useful method for two-site functionalization of the adjacent C(sp^2)-H bonds of olefins.

Conflicts of interest

There are no conflicts to declare.

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10 The products 3u and 3v contain a small amount of 3u' and 3v' products formed by the reaction of 2-hydroxy-1,4-naphthoquinone with another double bond of 2u and 2v.