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Rh(III)-catalyzed synthesis of dibenzo[*b*,*d*]pyran-6-ones from aryl ketone *O*-acetyl oximes and quinones *via* C–H activation and C–C bond cleavage†

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A redox-neutral synthesis of dibenzo[*b*,*d*]pyran-6-ones from aryl ketone *O*-acetyl oximes and quinones has been realized *via* Rh(III)-catalyzed cascade C–H activation annulation. A possible Rh(III)–Rh(V)–Rh(III) mechanism involving an unprecedented β-C elimination step was proposed.

The dibenzo[*b*,*d*]pyran-6-one is one of the most important structural motifs widely present in natural products with pharmacological relevance,[1] such as gut microbiota metabolites urolithins (**1–4**) that show anti-inflammatory, antiglycative and neuroprotective effects,[2–4] and the extracts of an endophytic fungus *Cephalosporium acremonium* IFB-E007 (**5–7**) that have pronounced anticancer activities.[5] In addition, the related heterocyclic structure benzo[*d*]naphtho[1,2-*b*]pyran-6-one is found in some bactericidal and antitumor natural products including gilvocarcins[6,7] (**8–10**) chrysomycins[8,9] (**11–13**), *etc.* (Fig. 1). Therefore, a number of approaches to access dibenzo[*b*,*d*]pyran-6-ones have been developed *via* the intra- or intermolecular biaryl formation as the key step.[10] However, many of these methodologies require multi-step reactions, and the development of new efficient synthetic methods, especially those easy one-step reactions that are still of great interest.

In the past decade, transition-metal-catalyzed C–H bond activation has proven to be a powerful tool in organic syntheses[11] and several methods for the synthesis of dibenzo[*b*,*d*]pyran-6-ones *via* C–H activation have been reported.[12] Actually, in 2015, our group reported Rh(III)-catalyzed synthesis of dibenzo[*b*,*d*]pyran-6-ones from *N*-methoxybenzamides and quinones through C–H activation annulation.[13] Interestingly, we obtained the same products using aryl ketone *O*-acetyl oximes as substrates to react with quinones under Rh(III)-catalyzed conditions in this work. Rh(III)-catalyzed C–H activation using ketoximes as substrates has been developed for synthesis of various substituted heterocycles.[14] Compared to the previous reports, this reaction undergoes a novel mechanism involving an unexpected C–C bond cleavage, which is attractive. Moreover, our study demonstrated that solvent is vital to these reactions. In 2018, we reported Rh(III)-catalyzed annulation of aryl ketone *O*-acetyl oximes with quinones to synthesize 6*H*-benzo[*c*]chromenes with acetone as a co-solvent.[15] Herein, we described Rh(III)-catalyzed synthesis of dibenzo[*b*,*d*]pyran-6-ones using the same substrates without acetone (Scheme 1).

Initially, the reaction of acetophenone *O*-acetyl oxime **1a** with benzoquinone **2a** was employed to optimize the reaction conditions (Table 1). When the reaction was conducted in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%) and PivOH (100 mol%) in MeOH at 50 °C for 12 h, 2-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one **3a** was obtained in 12% yield (Table 1, entry 1). Elevating the reaction temperature led to a higher yield of **3a** (Table 1, entries 1–4). Solvent screening (Table 1, entries 4–9) revealed that reaction in MeOH gave a higher yield of **3a** (Table 1, entry 4). Among the additives tested, benzoic acid was the most favorable with respect to product yield (Table 1, entries

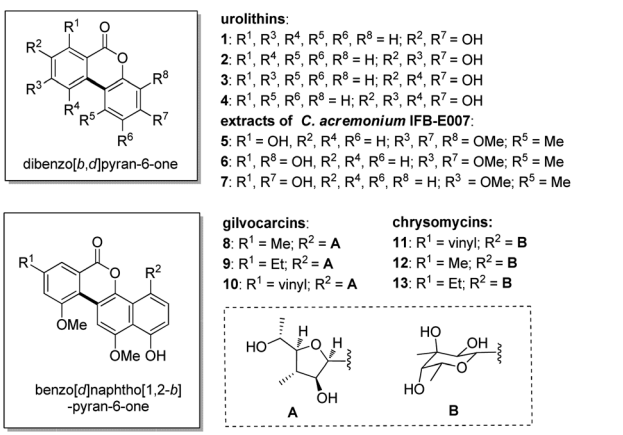

Fig. 1 Selected representative natural products.

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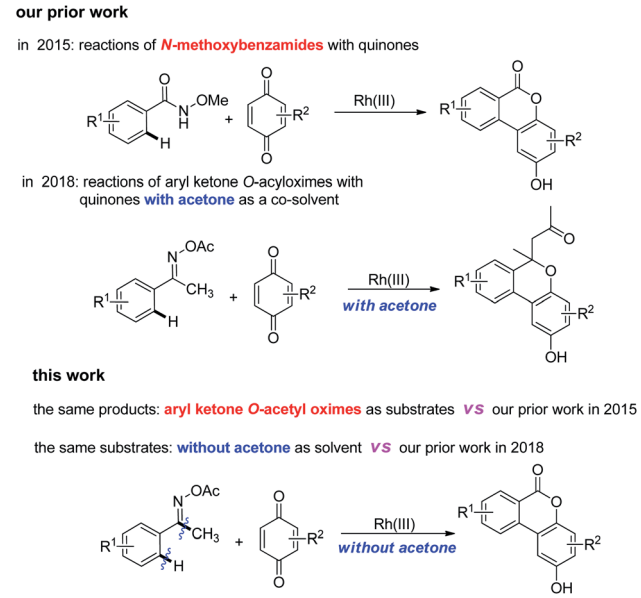
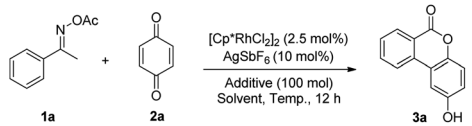


Scheme 1 Rh(III)-catalyzed divergent C–H activation annulation with quinones.

Table 1 Optimization of the reaction conditions[a]



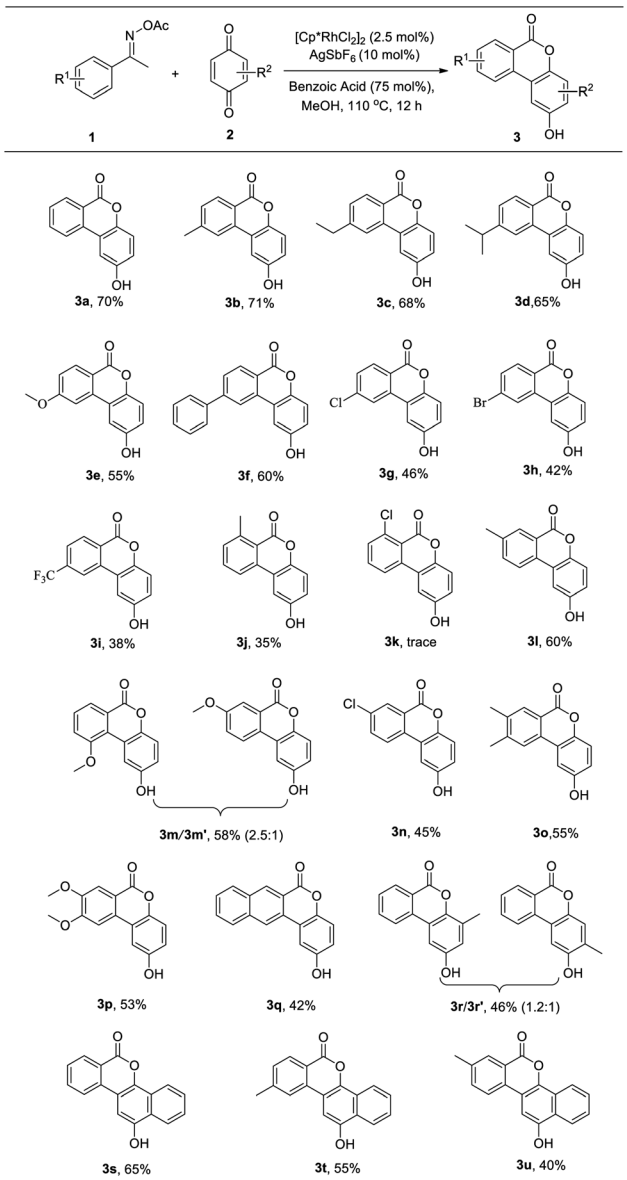
Entry	Additive	Solvent	Temp °C	Yield[b] (%)
1	PivOH	MeOH	50	12
2	PivOH	MeOH	70	20
3	PivOH	MeOH	90	36
4	PivOH	MeOH	110	43
5	PivOH	EtOH	110	26
6	PivOH	DMF	110	37
7	PivOH	THF	110	16
8	PivOH	HFIP	110	0
9	PivOH	Acetone	110	Trace
10	HOAc	MeOH	110	Trace
11	Benzoic acid	MeOH	110	50
12[c]	Benzoic acid	MeOH	110	70
13[d]	Benzoic acid	MeOH	110	63

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), additive (100 mol%), solvent (1 mL) for 12 h. [b] Isolated yields. [c] Benzoic acid (75 mol%) was added. [d] Benzoic acid (50 mol%) was added.

4, 10 and 11). Decreasing the amount of benzoic acid to 75 mol% resulted in the best yield of **3a** (Table 1, entry 12).

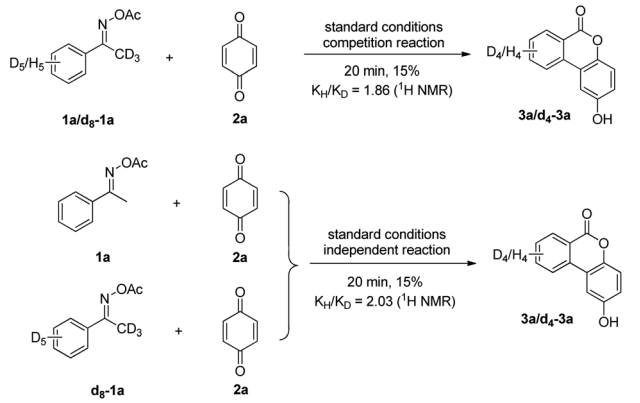
Under the obtained optimum reaction conditions above (Table 1, entry 12), we surveyed the reaction scope (Table 2). First, the reactions of various aryl ketone *O*-acetyl oximes **1** with **2a** were examined. For acetophenone *O*-acetyl oximes, substrates with electron-donating groups or phenyl at the *para*-

Table 2 The reaction scope[a]

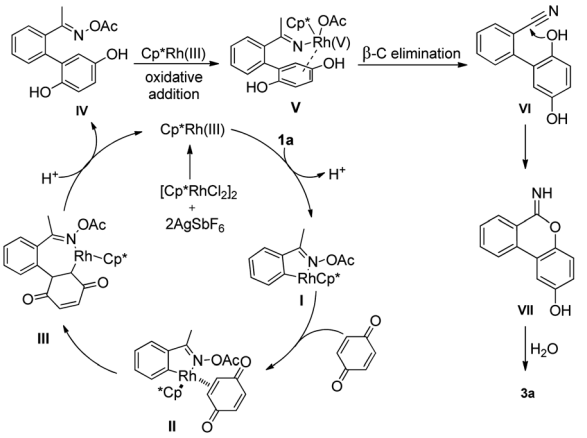


[a] Standard conditions.

position of aryl groups participated well in this reaction and the corresponding products were obtained in good yields (**3a–3f**). Substrates with halogens or strong electron-withdrawing group trifluoromethyl gave the products in lower yields (**3g–3i**). Substrate bearing the methyl or chlorine at the *meta*-position provided the desired products **3l** and **3n** with exclusive regioselectivity toward the less-hindered site, whereas the *meta*-methoxy-substituted derivative gave a mixture of regioisomers (**3m**/**3m**′ = 2.5 : 1), revealing that the nature of the substituent at the *meta*-position had an effect on the regioselectivity. 3,4-Disubstituted acetophenone *O*-acetyl oximes smoothly reacted to result the corresponding dibenzo[*b*,*d*]pyran-6-ones **3o** and **3p** in moderate yields. 2-Acetonaphthone *O*-acetyl oxime also produced the target product 2-hydroxy-6*H*-naphtho[2,3-*c*]



Scheme 2 Kinetic isotope effect experiments.



Scheme 3 Proposed mechanism.

chromen-6-one **3q**. Next, we examined the reactivity of quinone derivatives with **1a** under the established conditions. Methyl benzoquinone afforded the desired molecule in 46% yield with regioisomers (**3r**/**3r′**) in a ratio of approximately 1.2 : 1. The naphthoquinone could be also well tolerated, giving benzo[*d*] naphtho[1,2-*b*]pyran-6-one **3s** in 65% yield. Furthermore, *para*-methyl-substituted or *meta*-methyl-substituted acetophenone *O*-acetyl oximes also smoothly reacted with naphthoquinone to give the corresponding products **3t** or **3u**. Thus, several tetracyclic benzo[*d*]naphtho[1,2-*b*]pyran-6-ones were synthesized successfully.

To shed light on the reaction mechanism of this annulation, the reaction of acetophenone *O*-acetyl oxime **1a** with benzoquinone **2a** under standard conditions was detected by GC-MS, and benzonitrile was observed (detected by GC-MS; see ESI†). This result suggested this reaction might undergo a β-C elimination. Then, deuterium-labeling experiments were further carried out to gain some insights into the catalytic mechanism. A competition between protio and deutero **1a** showed a KIE value of 1.86 at early conversion. The KIE was further measured from two side-by-side reactions using protio and deutero **1a** with **2a** and a KIE value of 2.03 was observed (Scheme 2). These results demonstrated that the C–H bond cleavage process might be involved in the rate-determining step.

On the basis of our previous work, present observations and literature precedent,[11,13,15,16] a mechanistic pathway is proposed (Scheme 3, taking the reaction of substrate **1a** with benzoquinone **2a** as an example). First, *O*-acetyl oxime **1a** reacts with the active Cp*Rh(III) species through directed C–H cleavage to form a five-membered rhodacycle intermediate **I**. Next, coordination of the benzoquinone affords intermediate **II**, which undergoes migratory insertion into the incipient Rh–C bond to form a seven-membered rhodacycle **III**. Protonolysis and aromatization deliver biaryl intermediate **IV**. Then, an oxidative addition of Rh(III) into the O–N bond is possible to produce the Rh(V) species **V**,[17] followed by β-C elimination to give the intermediate **VI**.[18] A subsequent intramolecular nucleophilic addition of intermediate **VI** delivers the intermediate **VII**, which undergoes hydrolysis to generate the final product **3a**.

Conclusions

In summary, we have developed a novel Rh(III)-catalyzed cascade C–H activation annulation with readily available and inexpensive substrates for the convenient and direct synthesis of dibenzo[*b*,*d*]pyran-6-ones. In this process, we proposed a possible Rh(III)–Rh(V)–Rh(III) pathway, which might undergo an unprecedented β-C elimination step. This is the first example of β-C elimination *via* Rh(III)-catalyzed C–H bond functionalization. Further studies into the detailed reaction mechanism is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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