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Construction of Highly Functionalized Xanthones via Rh-Catalyzed Cascade C−H Activation/*O*-Annulation

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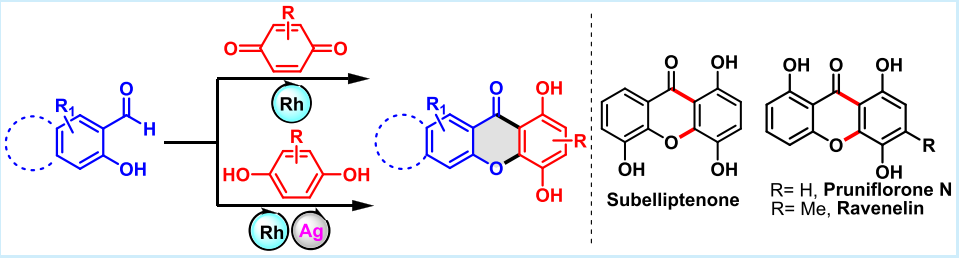

ABSTRACT: A facile and efficient strategy for obtaining functionalized and multihydroxylated xanthones via Rh catalysis under redox-neutral conditions is developed. Diverse salicylaldehydes bearing heterocycles, aromatics, and fused aromatics can be rapidly coupled with 1,4-benzoquinones or 1,4-hydroquinones to afford valuable xanthones via cascade C−H/O−H functionalization and annulation. This protocol provides a rapid synthetic approach to obtain biologically active materials through late-stage functionalization and prepares natural products such as subelliptenone, pruniflorone N, and ravenelin.

Xanthones are oxygen-containing heterocycles that are widely found in synthetic and natural products.[1,2] These compounds exhibit excellent biological[3] and pharmacological activities,[4] and some of these are used as major drug candidates.[5,6] In particular, multihydroxylated xanthones bearing 1,4-dihydroxyl groups have shown anticancer, antidiabetic, antiplasmodial, antimicrobial, and anti-inflammatory activities.[7,8] Owing to their biological activities, a number of synthetic procedures for preparing xanthone skeletons, including biosynthetic approaches, have been reported.[9,10] Among these, the representative strategies include Cu-catalyzed couping of 2-nitrobenzaldehydes with phenols (Scheme 1a),[11] Rh- and Fe-catalyzed intramolecular cross-dehydrogenative coupling of 2-aryloxybenzaldehydes (Scheme 1b),[12] and base-promoted tandem reaction of alkynylchromones with 1,3-dicarbonyl compound (Scheme 1c).[13] However, there are no examples of the direct preparation of biologically interesting multihydroxylated xanthones bearing chiral moieties, polycyclic rings, and polyaromatic rings.

Recently, direct aldehyde C−H functionalization of salicylaldehyde has been employed as a versatile tool in organic synthesis.[14−18] Neverthless, no studies have investigated the synthesis of xanthones via transition-metal-catalyzed aldehydic C−H activation of salicylaldehydes with readily available coupling partners. In 2018, our group developed a novel methodology for the construction of diverse xanthones via base-promoted benzannulation reaction of *N*-tosylhydrazones with 3-formylchromones.[19] This protocol made it difficult to synthesize polyhydroxylated xantone with chiral moieties, polycyclic rings, and polyaromatic rings. To

Scheme 1. Prior Work in the Context of the Present Study

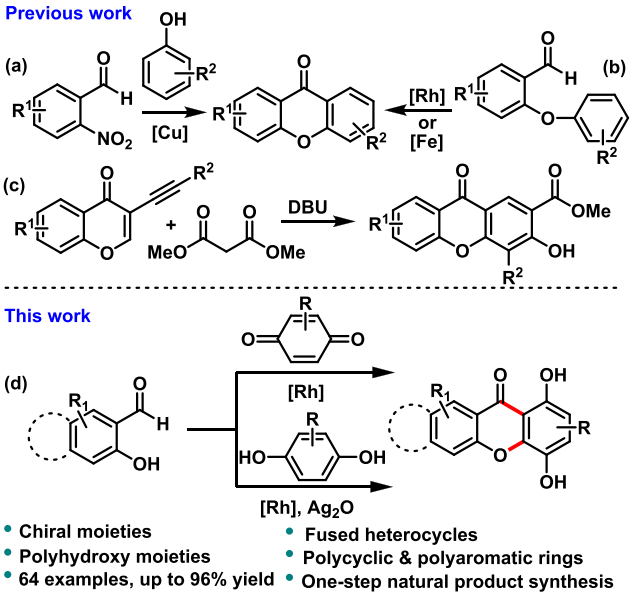

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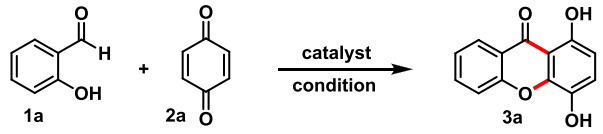
Table 1. Optimization of Reaction Conditions for 3a[a]



entry	catalyst (5 mol %)	additive (mol %)	solvent	time (h)	yield[b] (%)
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$ (20)	DCE	24	0
2	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$ (100)	DCE	12	25
3	$[Cp^*RhCl_2]_2$	Ag_2CO_3 (100)	DCE	12	27
4	$[Cp^*RhCl_2]_2$	AgOAc (100)	DCE	12	56
5	$[Cp^*RhCl_2]_2$	NaOAc (100)	DCE	12	70
6	$[Cp^*RhCl_2]_2$	CsOAc (100)	DCE	12	75
7	$[Cp^*RhCl_2]_2$	CsOAc (100)	toluene	12	35
8	$[Cp^*RhCl_2]_2$	CsOAc (100)	THF	12	39
9	$[Cp^*RhCl_2]_2$	CsOAc (100)	^{t}AmOH	12	22
10	$[Cp^*RhCl_2]_2$	CsOAc (100)	DMF	12	20
11[c]	$[Cp^*RhCl_2]_2$	CsOAc (100)	DCE	16	88
12		CsOAc (100)	DCE	24	0
13	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc (100)	DCE	24	0
14[c]	$[Rh_2Cl_2(COD)_2]$	CsOAc (100)	DCE	24	trace
15[c]	$[RhCl(PPh_3)_3]$	CsOAc (100)	DCE	24	trace
16	$[Cp^*IrCl_2]_2$	CsOAc (100)	DCE	24	20

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst, and additives in solvent (3.0 mL) for 16 h. [b]Isolated yields. [c]2.5 mol % of catalyst was used.

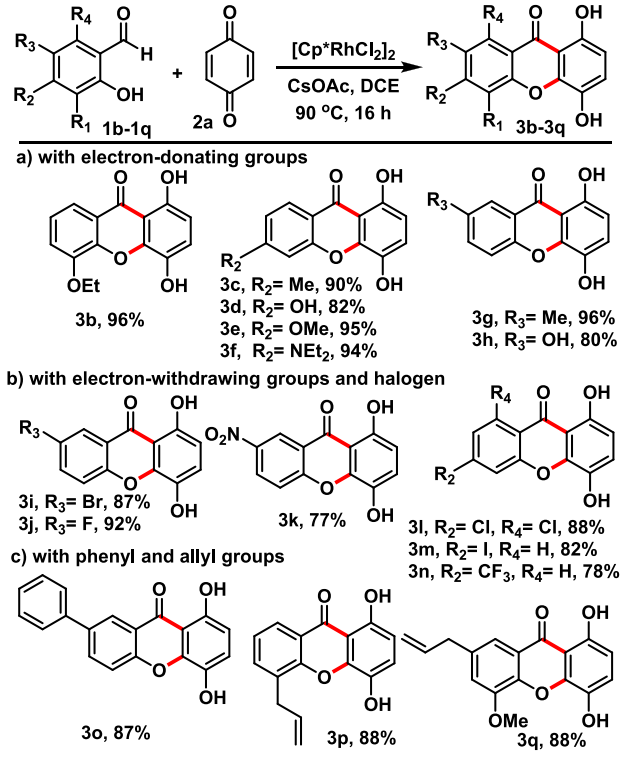
overcome the shortcoming, the development of new strategies is urgently required. This paper describes the first report for the direct preparation of divergent polyhydroxylated xanthones bearing chiral moieties, polycyclic rings, and polyaromatic rings via Rh-catalyzed double C−H/O-H functionalization of salicylaldehydes with 1,4-benzoquinones or 1,4-hydroquinones (Scheme 1d).

The initial reaction of salicylaldehyde (**1a**) and 1,4-benzoquinone (**2a**) with $[Cp^*RhCl_2]_2$ and $AgSbF_6$ at 80 °C in 1,2-dichloroethane (DCE) did not afford any products (Table 1, entry 1). When $Cu(OAc)_2$ was used as an additive, **3a** was produced in 25% yield (entry 2). Encouraged by this result, additives such as Ag_2CO_3, AgOAc, and NaOAc were tested (entries 3−5). The use of CsOAc increased the yield of **3a** up to 75% (entry 6). Interestingly, when the loading of the catalyst was decreased to 2.5 mol % at 90 °C, the product yield improved significantly (88%, entry 11). Changing the catalyst from Rh (III) to Ru(II), Rh(I), and Ir(III) failed to provide **3a** in good yield (entries 13−16).

Thereafter, the scope and generality of this protocol was investigated (Schemes 2 and 3). The reactions of **2a** with salicylaldehydes bearing electron-donating groups led to the formation of corresponding xanthones **3b**−**3h** in 80−96% yields. Similarly, salicylaldehydes with electron-withdrawing groups and halogens successfully furnished **3i**−**3n** in 77−92% yields. Salicylaldehydes bearing 5-phenyl, 3-allyl, and 5-allyl-3-methoxy groups participated smoothly in the reactions (**3o**−**3q**) to afford the corresponding xanthones in 87−88% yields. Notably, the reactions of salicylaldehydes with heterocyclic rings provided xanthones containing bioactive 2,2-dimethyl-2*H*-chromene, flavone, and carbazole moieties in excellent yields (**4a**−**4c**, Scheme 3). Salicylaldehydes with heteroaromatic rings and fused aromatic rings led to the formation of desired xanthones (**4d** and **4e**) and benzoxanthones (**4f**−**4j**).

To diversify the scope of this protocol, various substituted 1,4-benzoquinones were tested (Scheme 4). Symmetrically

Scheme 2. Annulation of Salicylaldehydes with Benzoquinones



substituted 1,4-benzoquinones were reacted with salicylaldehydes bearing electron-donating and electron-withdrawing groups (**5a**−**5e**). Unsymmetrically substituted 2-methyl-1,4-benzoquinone afforded two products **5f** and **5f′** as regioisomers in 65% and 20% yields, respectively. Similar observations were made for **5g** and **5h**. Despite the different stereoelectronic characteristics of the substituents on the

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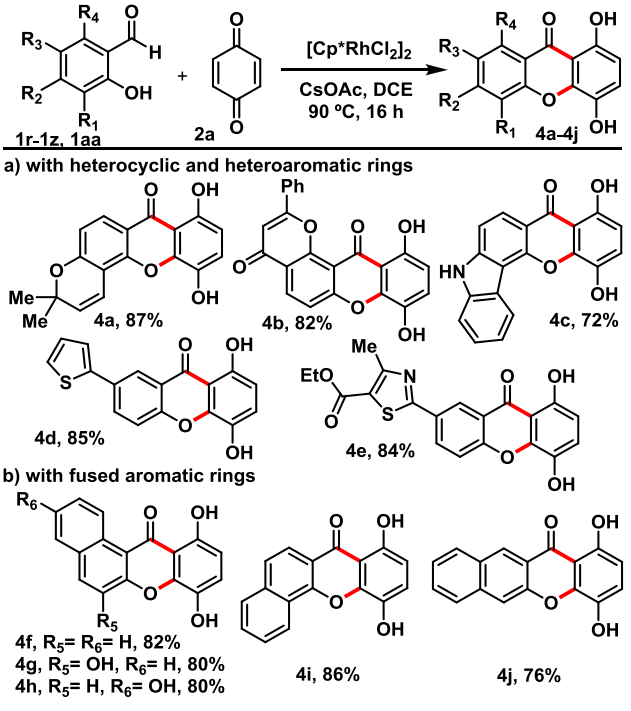
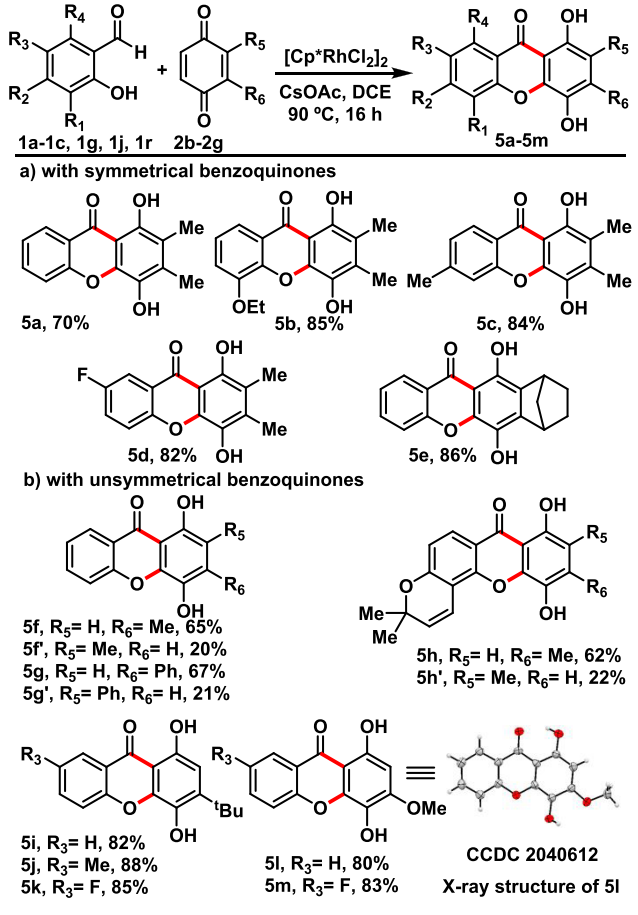
Scheme 3. Annulation with Heterocyclic and Polyaromatic Rings



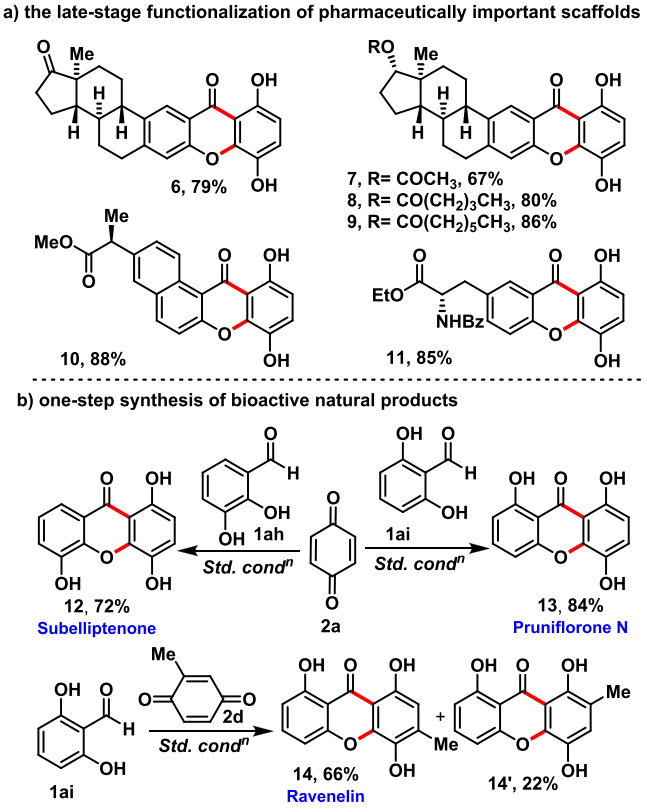
Scheme 4. Substrate Scope of Substituted 1,4-Benzoquinones



unsymmetrical 1,4-benzoquinones, the reactions afforded the desired products in good to excellent regioselectivity. Remarkably, unsymmetrically substituted 1,4-benzoquinones bearing electron-donating groups such as bulky 2-*tert*-butyl and 2-OMe led to products **5i**−**5m** (80−88%) without the formation of minor regioisomers. X-ray analysis confirmed the structure of **5l** (CCDC 2040612).

Subsequently, the late-stage functionalization of pharmaceutically important scaffolds using this methodology was examined (Scheme 5a). A xanthone bearing a biologically

Scheme 5. Late-Stage Functionalizations and One-Step Synthesis of Natural Products



interesting estrone moiety (**6**) was prepared in good yield (79%).[21] Similarly, the reaction of *ortho*-formylated derivatives of *β*-estradiol 17-acetate, *β*-estradiol 17-valerate, or *β*-estradiol 17-heptanoate with **2a** provided the corresponding xanthones **7**−**9** bearing *β*-estradiol nuclei.[21] Notably, this methodology was extended to the reactions of the chiral molecules derived from naproxen and *N*-benzoyl-L-tyrosine ethyl ester with **2a**, leading to the formation of biologically valuable compounds **10** (88%) and **11** (85%).[21] Inspired by the production of bioactive compounds in a single step using this method, the one-step synthesis of natural products was investigated (Scheme 5b). Subelliptenone (**12**) and pruniflorone N (**13**) have been isolated from *Garcinia subelliptica* and *Cratoxylum formosum* ssp. *pruniflorum*, respectively, and possess various biological and pharmacological properties including antimalarial, antibacterial, cytotoxic, and anti-inflammatory activities.[7a,b] Natural products **12** and **13** were obtained in preparative yields in a single step (Scheme 5). Ravenelin (**14**) is a xanthone pigment isolated from fungal species of *Helminthosporium ravenelii* and *H. Turcicum*.[7c,d] The reaction of dihydroxybenzaldehyde **1ai** with **2d** afforded ravenelin (**14**) in 66% yield and its

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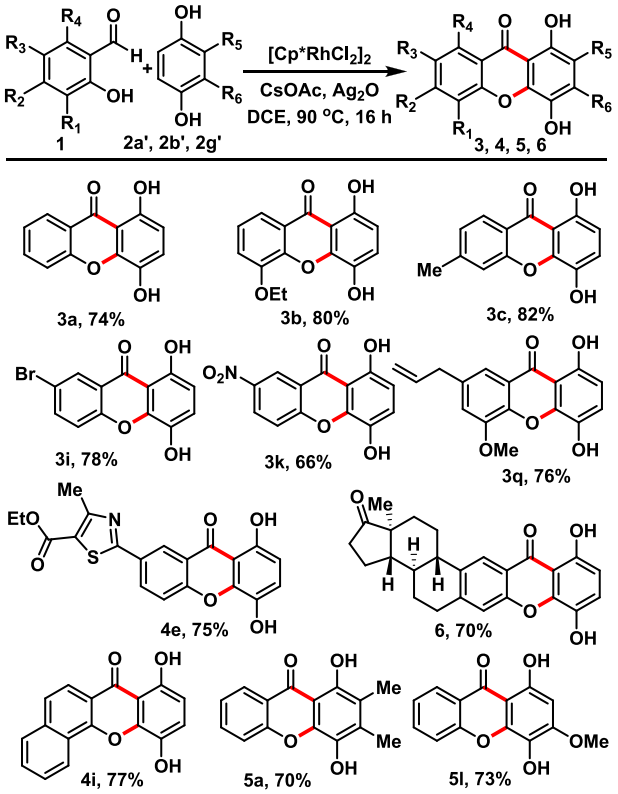
regioisomer **14′** in 22% yield. Further attempts to improve the yields by lowering the temperature (80 °C; **14** (53%) and **14′** (15%)) and decreasing the Rh catalyst amount (1 mol %; **14** (40%) and **14′** (12%)) were unsuccessful.

When salicylaldehyde was reacted with 1,4-hydroquinone (**2a′**) instead of 1,4-benzoquinone (**2a**), xanthone formation was not observed. However, when silver(I) oxide was added, **3a** was generated in 74% yield. The versatility of this protocol with 1,4-hydroquinone was tested (Scheme 6) with salicylaldehyde bearing electron-donating (**3b** and **3c**), electron-withdrawing (**3i** and **3k**), and other types of substituents (**3q**, **4e**, and **4i**). Interestingly, 1,4-hydroquinone was successfully employed for the late-stage functionalization of estrone (**6**) and by using substituted 1,4-hydroquinone (**5a** and **5l**).

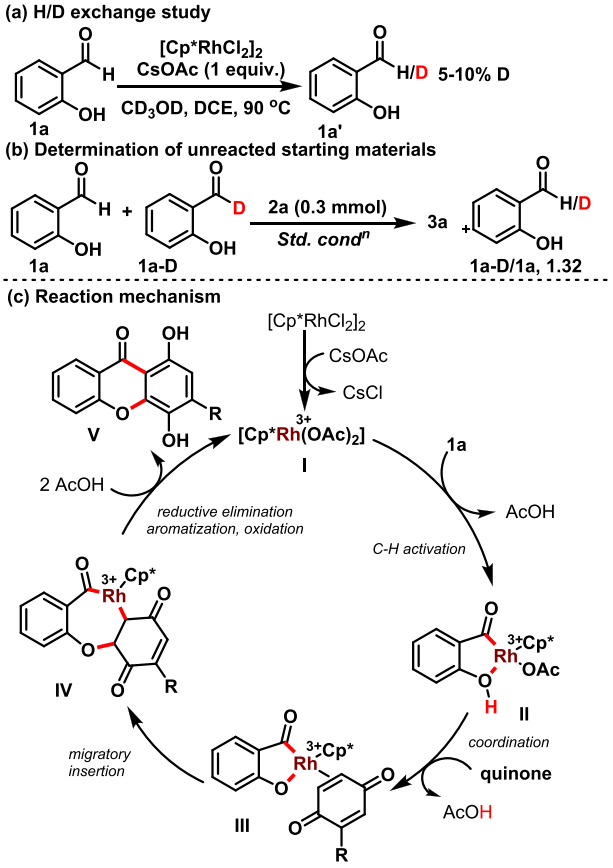
Scheme 6. Reaction with 1,4-Hydroquinones



To gain insights into the reaction mechanism, **1a** was treated with 1, 2, and 4 equiv of CD_3OD in 1,2-DCE under standard conditions; this treatment showed the deuteration of aldehydic C−H bond at 5, 8, and 10%, respectively (Scheme 7a). The competitive reaction between **1a** and **1a-D** was carried out in equimolar quantities. The unreacted mixture of **1a-D** and **1a** showed a ratio of 1.32 based on the ^{1}H NMR analysis (Scheme 7b).[21]

The combination of 2-methoxybenzaldehyde (or benzaldehyde) and 1,4-benzoquinone under standard conditions remained unreacted even after 16 h, indicating the importance of the *ortho* hydroxyl group. The more electron-deficient 2-(methoxycarbonyl)-1,4-benzoquinone or 2-(methoxycarbonyl)-1,4-hydroquinone did not provide the annulation product with salicylaldehyde. Similarly, 1,4-naphthoquinone, which is significantly electron deficient compared to 1,4-benzoquinone, did not undergo effective olefin coordination, resulting in no annulation reaction. When salicylaldehyde was reacted with 1,2-benzoquinone, catechol, or 1,2-naphthoquinone (instead of 1,4-benzoquinone), no annulation product was observed. These substrates are likely to bind rhodium in a bidentate chelating mode; therefore, olefinic coordination is improbable, and the desired catalysis cannot proceed. When the reaction was performed at high temperature (e.g., 130 °C), xanthone was still obtained as the only product, and decarbonylation or any other side product(s) was not observed.

Scheme 7. Control Experiments and Plausible Reaction Pathway



Based on the experimental observations and literature reports,[15−18] a plausible mechanism for this protocol is outlined in Scheme 7c. An active rhodium catalyst **I** is generated in the presence of CsOAc, which undergoes C−H metalation with **1a** to form five-membered rhodacycle intermediate **II** through hydroxyl-directed aldehydic C−H bond activation. The coordination of quinone with **II** generates intermediate **III**, which produces a seven-membered rhodacycle intermediate **IV** *via* migratory insertion. Next, Rh complex **IV** undergoes reductive elimination and aromatization to afford the final product **V** and Rh(I) catalyst. Rh(I) is oxidized to the active Rh(III) catalyst by air in combination with benzoquinone and AcOH. The regenerated Rh(III) catalyst is further used to catalyze the next catalytic cycle.[20] Regiocontrol in unsymmetrically substituted 1,4-benzoquinones is governed by the stereoelectronic characteristics of the substituent, which in turn dictate the mode of migratory insertion.

In conclusion, one-step synthesis of diverse multihydroxylated xanthone derivatives is developed via Rh(III)-catalyzed double C−H/O−H annulation of the salicylaldehydes with 1,4-benzoquinones or 1,4-hydroquinones. This redox-neutral

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protocol affords a broad substrate scope, excellent functional group tolerance, and high product yield. Although some aspect of the present protocol can be improved to render the method green,[22] the synthetic potential of this protocol is newly established for the late-stage functionalization of estrone and its derivatives, naproxen and L-tyrosine ethyl ester. Moreover, the natural products subelliptenone, pruniflorone N, and ravenelin are synthesized in a single step, demonstrating the versatility and practicality of this method. Sustainable C−H activation methodologies for the direct construction of natural products from cheap and easily available precursors are currently under study.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00391.

General procedures, compound characterization, and copies of NMR spectra of all products; X-ray data for **5l** (PDF)

FAIR data, including the primary NMR FID files, for compounds **1ab−1ag**, **1s**, **1t**, **1x**, **1y**, **3a−3q**, **4a−4j**, **5a−5m**, **6−14**, and **14′** (ZIP)

Accession Codes

CCDC 2040612 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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