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Ruthenium-catalyzed C–H oxygenation of quinones by weak O-coordination for potent trypanocidal agents†
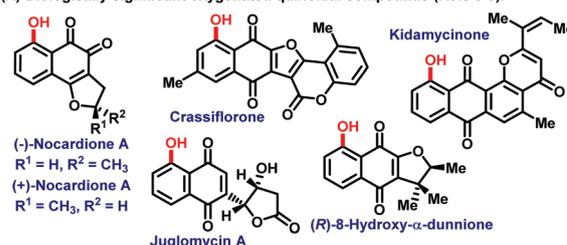
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Ruthenium-catalysis enabled the C-5 selective C–H oxygenation of naphthoquinones, and also sets the stage for the site-selective introduction of a hydroxyl group into anthraquinones. A-ring modified naphthoquinoidal compounds represent an important class of bioactive quinones for which the present study encompasses the first C–H oxygenation strategy by weak O-coordination.
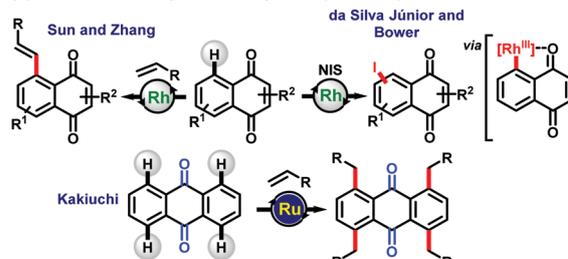
Among the versatile scaffolds studied in Medicinal Chemistry, quinones represent a privileged class of substance.[1] Thus, quinoidal compounds are involved in biologically relevant processes, such as in the electron transport chain, redox mediators, and as alkylating agents in a broad spectrum of biological processes.[2] For example, nocardiones A are notable bioactive naphthoquinoidal molecules. (−)-Nocardione A is a Cdc25B tyrosine phosphatase inhibitor, while (+)-nocardione A presents antifungal and cytotoxic activity with the ability to kill human myeloid leukemia cell lines *via* a mechanism of action associated with apoptosis.[3] Remarkable 1,4-naphthoquinones (1,4-NQs) include crassiflorone,[4] a natural product isolated from the stem bark of the African ebony (persimmon) tree *Diospyros crassiflora* with anti-mycobacterial and anti-gonorrhoeal properties,[5] among others. Furthermore, juglomycin A,[6] (*R*)-8-hydroxy-*R*-dunnione[7] and kidamycinone[8] are examples of important quinoidal compounds with diverse bioactivity[9] (Scheme 1A).

The quinones depicted in Scheme 1A bear a hydroxyl group as a recurring structural motif in the benzenoid A-ring, which is
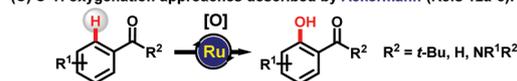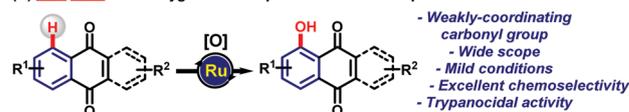

Scheme 1 Overview.

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usually installed in the first steps of their previously reported respective syntheses.[3,4,8] The preparation of such molecules *via* late-stage functionalization by C–H activation logic has thus far not been addressed.[10] This C–H activation strategy can be an instrument to maximize the synthesis process with the preparation of the target molecules in a reduced number of steps with overall significantly improved yields. Late-stage functionalization of quinones is not easily achieved due to the following aspects, including: (a) generally deactivated quinoidal systems present low nucleophilicity at the benzenoid A-ring; (b) the

Table 1 Optimization of C–H oxygenation[a]
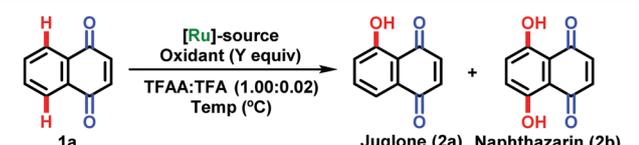
Entry	[Ru]-Source (mol%)	Oxidant	Y	Temp (°C)	2a	2b
1	[RuCl$_2$(*p*-cymene)]$_2$ (5)	PIFA	2.0	110	53	42
2	[RuCl$_2$(*p*-cymene)]$_2$ (2)	PIFA	1.2	80	87	5
3	[RuCl$_2$(*p*-cymene)]$_2$ (2)	PIDA	1.2	80	71	Traces
4	[RuCl$_2$(*p*-cymene)]$_2$ (2)	NH$_4$S$_2$O$_8$	1.2	80	NR	NR
5	RuCl$_3$·H$_2$O (5)	PIFA	1.2	80	NR	NR
6	[RhCp*Cl$_2$]$_2$ (5)	PIFA	1.2	80	NR	NR
7	CoCp*(CO)I$_2$(5)	PIFA	1.2	80	NR	NR
8	Pd(OAc)$_2$ (5)	PIFA	1.2	80	NR	NR
9[b]	—	PIFA	1.2	80	NR	NR
10[b]	**[RuCl$_2$(*p*-cymene)]$_2$ (2)**	**PIFA**	**1.2**	**80**	**92**	**3**

[a] General reaction conditions: (**1a**) (0.4 mmol), PIFA (0.5 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (5.0 or 2.0 mol%); (TFAA) (1 mL) and TFA (0.02 mL), 18 h. [b] 12 h. PIFA = PhI(CF$_3$CO$_2$)$_2$. PIDA = PhI(CH$_3$CO$_2$)$_2$. NR = for all cases starting material **1a** was recovered, with the exception of the reaction with Pd(OAc)$_2$, here degradation of the products was observed. Yields of isolated products.

weakly coordinating ability of the B-ring carbonyls towards transition metal catalysts and (c) the difficulty in developing general reaction protocols capable of providing favorable results with the use of different classes of quinonoid systems.[10]

In this context, Sun and Zhang, Kakiuchi, Bower and da Silva Júnior groups[11] have recently developed useful methods for C–H functionalization of naphthoquinones and anthraquinones (Scheme 1B). Despite the recent development in the area, direct

C–H oxygenations of quinonoid compounds have been proven to be elusive. Given our recent success in terms of ruthenium-catalyzed C–H oxygenations with weakly coordinating ketones, amides and aldehydes[12] (Scheme 1C), herein, we describe an efficient process for the direct, site-selective installation of a hydroxyl group in a broad range of naphthoquinones and anthraquinones. For the first time, a C–H bond oxygenation strategy was thus established for the synthesis of quinonoid derivatives with unique bioactivity (Scheme 1D).

Preliminary studies involved the reaction of 1,4-naphthoquinone (**1a**) with PhI(CF$_3$CO$_2$)$_2$ (PIFA) as an oxidant and [RuCl$_2$(*p*-cymene)]$_2$ as the catalyst (Table 1, entry 1). Here, juglone (**2a**) and naphthazarin (**2b**) were obtained in 53 and 42% yield, respectively. Further refinement aiming at minimizing the amount of the ruthenium-based catalyst afforded products **2a** and **2b** in 87 and 5% yield when 2 mol% of [RuCl$_2$(*p*-cymene)]$_2$ and 1.2 equivalents of PIFA were used (entry 2). Despite the efficiency of the catalyst, we continued our efforts towards alternative oxidation sources. Hence, PIDA and NH$_4$S$_2$O$_8$ were also evaluated as oxygenation agents, albeit with limited success (entries 3 and 4). We also tested alternative sources of catalysts with the use of rhodium, cobalt and palladium complexes, but promising results were not observed (entries 5–8). A control experiment confirmed the essential role of the ruthenium catalyst (entry 9). Fine tuning of the reaction temperature enabled the formation of juglone (**2a**) in 92% yield (entry 10). Viable substrates for the new C–H oxygenation strategy are outlined in Scheme 2.

Structural assignments were based on detailed NMR analysis and X-ray diffraction analysis of products **2c–2f**, **2h**, **2i** and **2j**.
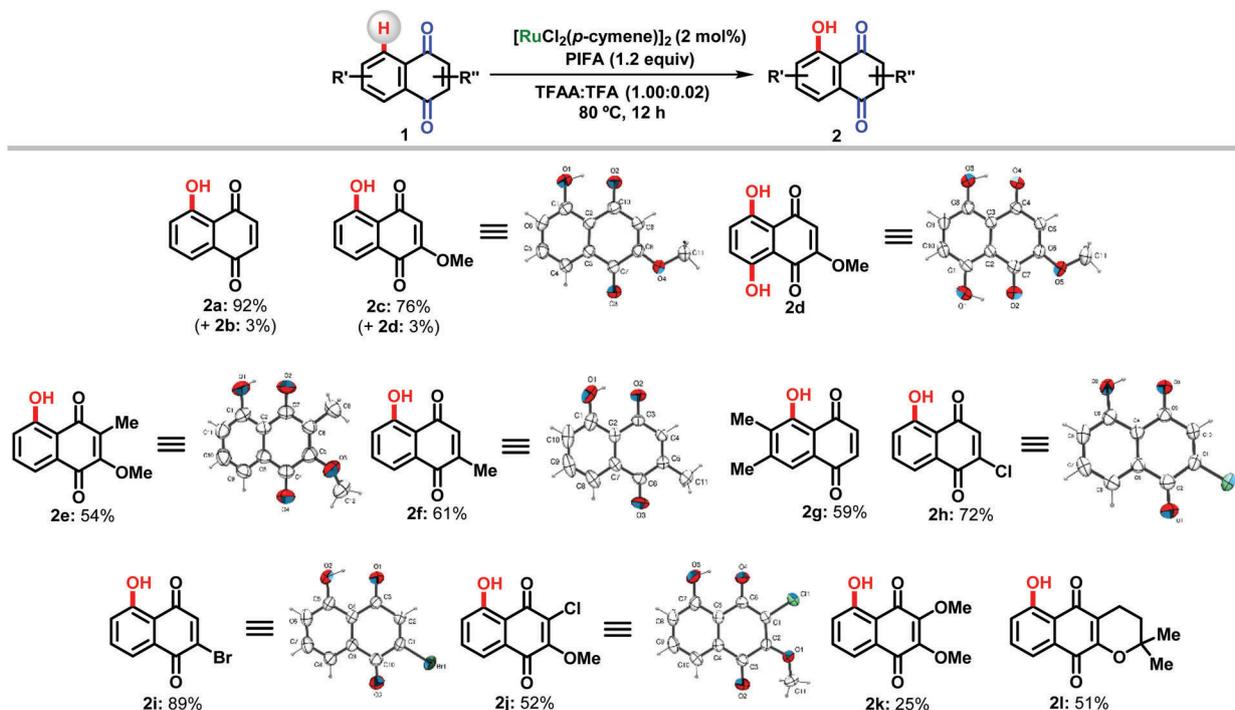
**Scheme 2** Scope of the naphthoquinone C-5 oxygenation protocol.

In general, quinones were prepared in moderate to high yields, tolerating the presence of electron withdrawing and donating groups. In most cases, the dihydroxylated product was not formed or was observed in only 3% yield (**2b** and **2d**). Our method proved effective even for the preparation of the hydroxylated derivative of α-lapachone (**2l**), a natural product related to the lapachol family with remarkable antitumor activity.[13]

Subsequently, the synthetic utility of the ruthenium(II)-catalyzed C–H oxygenation was reflected by the chemo-selective diversification of anthraquinones **3**. Here, a slight modification of the reaction conditions featured the use of PIDA, allowing for the C–H oxygenations with excellent levels of positional and chemo-selectivities in terms of mono-functionalization, fully tolerating, *inter alia*, chloro and bromo functional groups (Scheme 3).

Based on our previous reports, a plausible catalytic cycle is initiated by carboxylate-assisted C–H ruthenation,[12,14] along with subsequent oxidation-induced reductive elimination (Scheme 4).[14,15]

Neglected tropical diseases (NTDs) comprehend a group of seventeen illnesses that affect more than one billion people. Among NTDs, Chagas disease caused by the hemoflagellate protozoa *Trypanosoma cruzi* presents significant mortality and morbidity, especially in low-income populations in Latin America endemic countries.[16,17] Recently, the intense flux of immigration due to globalization has changed the distribution of Chagas disease patients, resulting in the presence of infected people in non-endemic countries such as European countries, the United States, Japan or Australia, where the transmission is sustained by blood transfusion or congenital routes.[18,19] Since the 1960s up to now, the clinical chemotherapy for Chagas disease has been based on two nitroderivatives, benznidazole and nifurtimox, that present important side effects and debatable anti-*T. cruzi* activity in chronic patients.[20] The absence of alternatives for the most severe phase of this illness leads to the continuous search for novel trypanocidal drugs.[21] In this context, in the last few years, we have evaluated diverse naphthoquinones against the parasite and proved the potential trypanocidal effect of
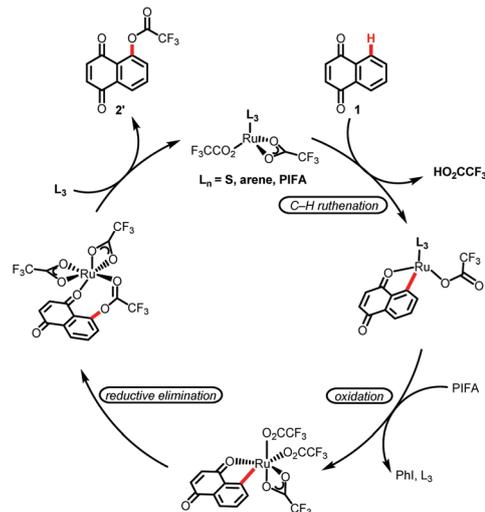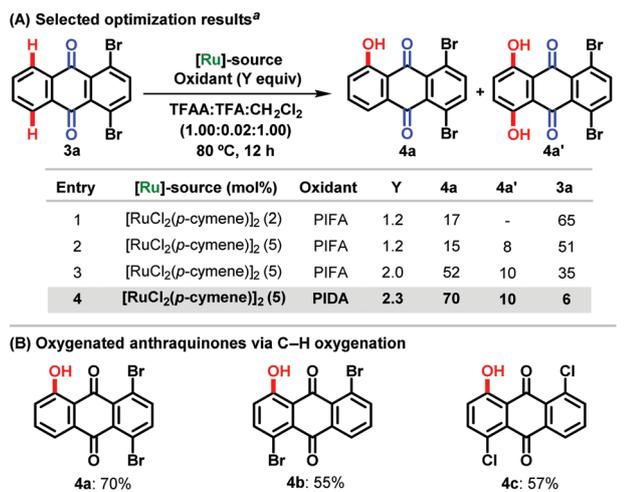

Scheme 4 Proposed mechanism.

these compounds.[11f] To understand the biological importance of A-ring modified quinoidal compounds and to continue our efforts towards the development of potent trypanocidal agents, we herein disclose the evaluation of 1,4-NQs against *T. cruzi*. Thus, compounds **2c**, **2e**, **2k** and **2l** were not active against the parasite with $IC_{50}/24$ h > 1000.0 μM. To our delight, six compounds showed activity against *T. cruzi* with IC_{50} in the range of 176.1 to 29.5 μM (Table S1), highlighting **2h** (IC_{50} = 32.9 μM) and **2i** (IC_{50} = 29.5 μM). In comparison with the standard drug benznidazole (IC_{50} = 103.6 μM), **2h** and **2i** are 3.1 and 3.5-fold more active, respectively (Fig. 1).

In conclusion, we have reported on an efficient C–H oxygenation strategy for naphthoquinones and anthraquinones. Thus, carboxylate-assisted[22] ruthenium(II) catalysis enabled the step-economical synthesis of potent bioactive compounds with ample scope. The obtained C–H hydroxylated naphthoquinones displayed unique trypanocidal activities.

Scheme 3 Synthesis of anthraquinone derivatives.

(A) Selected optimization results[a]

Entry	[Ru]-source (mol%)	Oxidant	Y	4a	4a'	3a
1	[RuCl₂(p-cymene)]₂ (2)	PIFA	1.2	17	–	65
2	[RuCl₂(p-cymene)]₂ (5)	PIFA	1.2	15	8	51
3	[RuCl₂(p-cymene)]₂ (5)	PIFA	2.0	52	10	35
4	[RuCl₂(p-cymene)]₂ (5)	PIDA	2.3	70	10	6

(B) Oxygenated anthraquinones via C–H oxygenation

4a: 70%   **4b**: 55%   **4c**: 57%

[a] General reaction conditions: (**3a**) (0.3 mmol), PIDA (0.7 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %); (TFAA) (1 mL), TFA (0.02 mL) and CH₂Cl₂ (1 mL). Yields of isolated products.
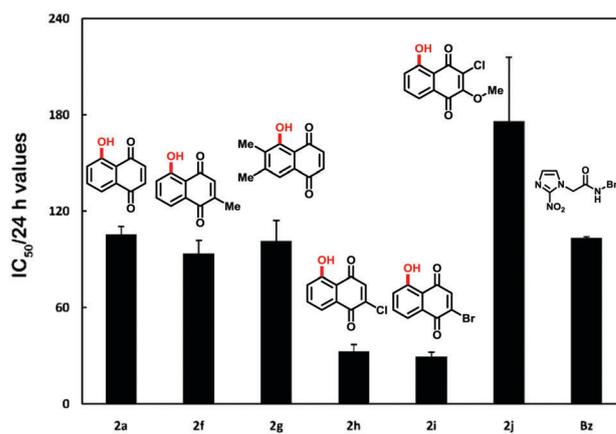

Fig. 1 Most active naphthoquinones on trypomastigote forms of *T. cruzi*. Benznidazole, a standard drug for the treatment of chagasic patients, was used as a control. $IC_{50}/24$ h values in μM.

Conflicts of interest

There are no conflicts to declare.

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