C–H Activation Hot Paper

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Aldehyde-Assisted Ruthenium(II)-Catalyzed C–H Oxygenations**

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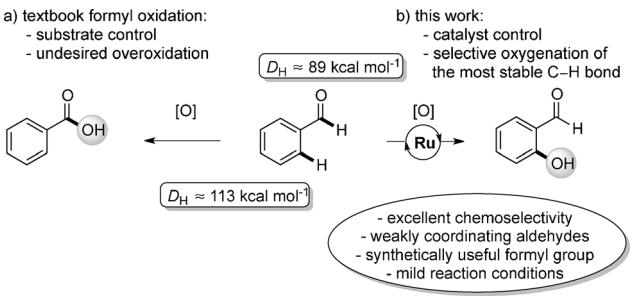
Abstract: *Versatile ruthenium(II) complexes allow for site-selective C–H oxygenations with weakly-coordinating aldehydes. The challenging C–H functionalizations proceed with high chemoselectivity by rate-determining C–H metalation. The new method features an ample substrate scope, which sets the stage for the step-economical preparation of various bioactive heterocycles.*

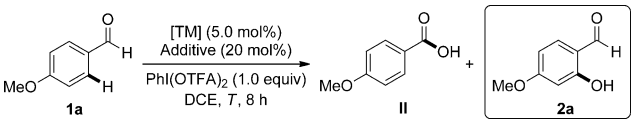
The catalytic functionalization of unactivated C–H bonds is an increasingly viable method for organic synthesis.[1] In particular, C–H activations that lead to the formation of C–O bonds have recently provided step-economical access to substituted phenols.[2] Chelation-assisted C–H oxygenations were accomplished with the assistance of pyridine, ketoxime, or amide groups, for example, mostly utilizing palladium, rhodium, or ruthenium catalysts.[1,2] C–H oxygenations with weakly coordinating directing groups pose a major challenge.[3,4] Notable recent progress was achieved by the use of ketones for site-selective C–H oxygenations.[5–7] In stark contrast, C–H oxygenations with significantly more challenging aldehydes have unfortunately proven elusive thus far, despite the unique utility of the formyl group in organic synthesis.[8,9] The lack of available C–H activation methods is likely due to the inherent tendency of aldehydes to undergo facile overoxidation under the strongly oxidizing reaction conditions of metal-catalyzed C–H functionalizations (Scheme 1 a). As part of our program on sustainable organic synthesis,[1b,10] we herein present the first aldehyde-directed C–H oxygenation, which proved viable with highly selective ruthenium(II)[11,12] catalysts (Scheme 1 b). Notably, the versatile ruthenium(II) catalysts override the inherent substrate-controlled formyl oxidation by chelation-controlled aromatic C–H activation.

At the outset of our studies, we probed the chemoselective C–H oxygenation of aldehyde **1a** (Table 1 and Table S1 in the Supporting Information). Preliminary experiments identified hypervalent iodine(III) reagents as the oxidants of choice. Among a variety of ruthenium complexes, [{$RuCl_2$(*p*-cymene)}$_2$] provided optimal results, notably in the absence of cocatalytic additives (entries 1–6), whereas the desired



Scheme 1. Chemoselectivity in the C–H activation of benzaldehyde.

Table 1: Optimization of the aldehyde-assisted C–H oxygenation.[a]



Entry	[TM]	Additive	*T* [°C]	Yield [%]		
				1a	**II**	**2a**
1	[{$RuCl_2$(*p*-cymene)}$_2$]	KOAc	80	44	32	5
2	[{$RuCl_2$(*p*-cymene)}$_2$]	$AgSbF_6$	80	51	9	15
3	[{$RuCl_2$(*p*-cymene)}$_2$]	KPF_6	80	35	3	39
4	[{$RuCl_2$(*p*-cymene)}$_2$]	–	80	32	9	43
5	[$RuCl_2(PPh_3)_3$]	–	80	51	16	5
6	$RuCl_3$	–	80	51	34	0
7	–	–	80	69	5	0
8	[{$RuCl_2$(*p*-cymene)}$_2$]	–	50	73	9	<2
9	[{$RuCl_2$(*p*-cymene)}$_2$]	–	100	26	3	47
10	[{$RuCl_2$(*p*-cymene)}$_2$]	–	120	26	3	40
11[b]	**[{$RuCl_2$(*p*-cymene)}$_2$]**	**–**	**100**	**12**	**2**	**72**
12[b]	$Pd(OAc)_2$	–	100	37	38	0
13[b]	[$Ni(acac)_2$]	–	100	79	14	0
14[b]	[{RhCp*Cl_2}$_2$]	–	100	70	11	0

[a] Reaction conditions: **1a** (0.5 mmol), [TM] (5.0 mol%), additive (20 mol%), PhI(OTFA)$_2$ (1.0 equiv), DCE (2.0 mL), 8 h. Yields of isolated products are given. [b] PhI(OTFA)$_2$ (1.5 equiv). acac = acetylacetonate, Cp* = pentamethylcyclopentadienyl, DCE = 1,2-dichloroethane, OTFA = trifluoroacetate.

product **2a** was not obtained without a ruthenium catalyst (entry 7). Superior results were obtained at a reaction temperature of 100 °C (entries 8–10) with PhI(OTFA)$_2$ as the terminal oxidant (entry 11). Intriguingly, the desired aldehyde-assisted C–H oxygenation was not accomplished with typical palladium, nickel, or rhodium C–H functionalization catalysts (entries 12–14)—a strong testament to the unique potential of mild ruthenium(II) catalysis.[13,14]

With the optimized reaction conditions in hand, we probed the scope of the aldehyde-assisted C–H oxygenation with diversely decorated substrates **1** (Scheme 2). A variety of *para*-substituted benzaldehydes **1b–k** provided the desired

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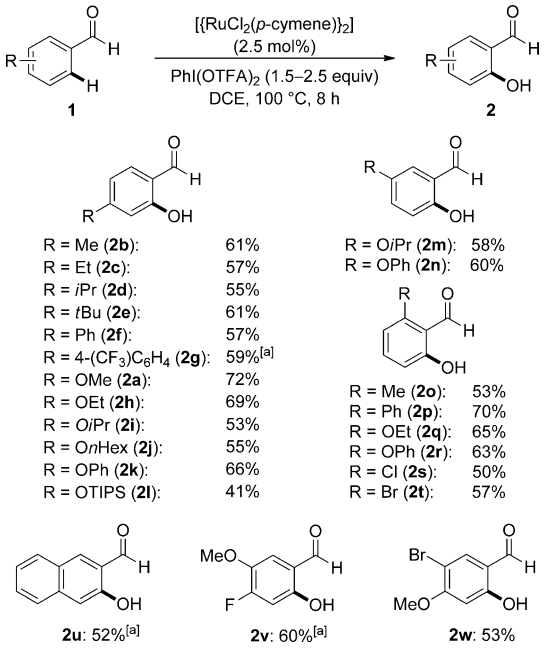


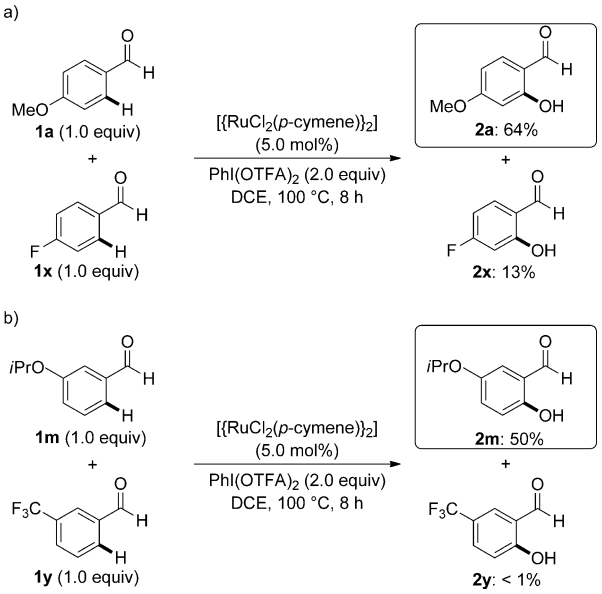
Scheme 2. Scope of the aldehyde-assisted C–H oxygenation. [a] [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol%).

products with high chemoselectivities. Substrates **1l** and **1m** displaying *meta* substituents gave the corresponding compounds **2l** and **2m** as the sole products with excellent site selectivity through functionalization of the less congested C–H bond. The more sterically hindered *ortho*-substituted arenes **1n–s** were converted with comparable catalytic efficacy, whereas useful electrophilic halide functional groups (F, Cl, Br) were well tolerated by the highly chemoselective ruthenium(II) catalyst.[15]

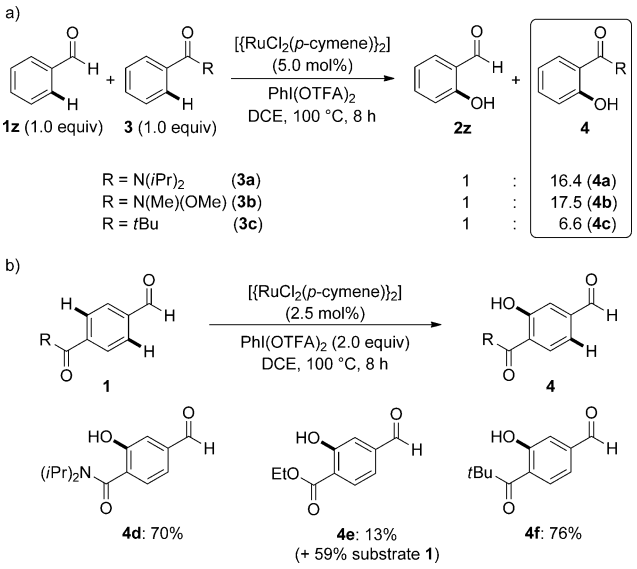
In light of the unique features of the aldehyde-assisted ruthenium catalysis, we performed mechanistic studies to delineate the catalyst's mode of action. To this end, intermolecular competition experiments between differently substituted substrates **1** indicated that electron-rich arenes inherently react preferentially (Scheme 3). This observation can, for instance, be rationalized in terms of an electrophilic base-assisted C–H ruthenation.[16]

Further intermolecular competition experiments between arenes with different directing groups clearly highlighted the challenges that are associated with the use of very weakly coordinating aldehydes (Scheme 4a). Namely, amides, Weinreb amides, and even ketones were identified as significantly more potent directing groups in the chelation-assisted C–H oxygenation. The excellent chemoselectivity was further reflected by intramolecular competition experiments (Scheme 4b).

Ruthenium-catalyzed C–H oxygenations with isotopically labelled substrate [D_4]-**1p** revealed in independent experiments an intermolecular kinetic isotope effect (KIE) of $k_H/k_D \approx 3.1$ (Scheme 5a), which is suggestive of a kinetically relevant C–H metalation step. The intramolecular KIE with substrate [D_1]-**1x** was determined to be $k_H/k_D \approx 4.3$ (Scheme 5b). The considerably different inter- and intramolecular KIEs strongly suggest formation of an intermediate in which



Scheme 3. Competition experiments with different aldehydes **1**.

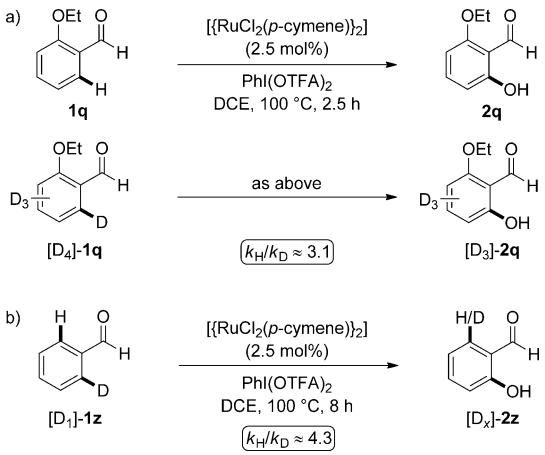


Scheme 4. Comparison of the directing group power.

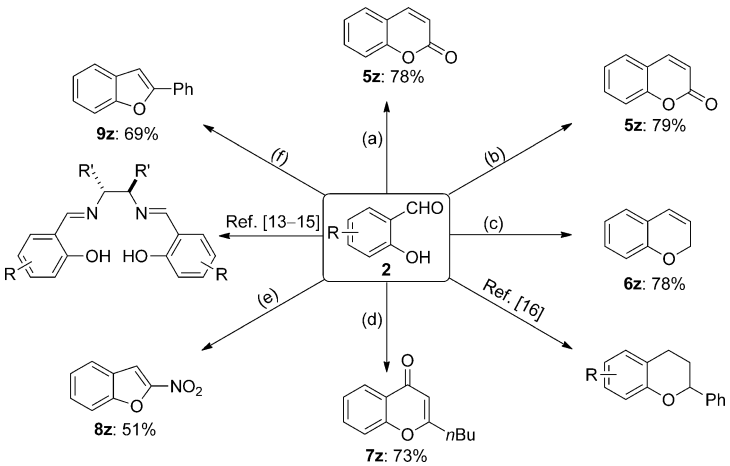
the aldehyde carbonyl group is pre-coordinated to the active ruthenium catalyst.[17]

Finally, we exploited the unique utility of the formyl group for the late-stage derivatization of the obtained C–H activation products **2**. Importantly, aside from salen-[18–20] or flavan-derived polyphenols,[21] a variety of bioactive heterocycles could be accessed in a step-economical fashion, including coumarin **5**, chromene **6**, benzopyran-4-one **7**, and the substituted benzofurans **8** and **9** (Scheme 6).[22,23]

In summary, we have reported the first C–H oxygenation by assistance of very weakly coordinating aldehydes. A user-friendly ruthenium(II) complex efficiently catalyzed the site-selective hydroxylation of various benzaldehydes with ample scope. The direct oxygenation occurred by a kinetically relevant C–H metalation, and the products thus obtained



Scheme 5. Studies of the kinetic isotope effect.



Scheme 6. Modification of products **2**. Reaction conditions: a) 1) Ph_3PCH_3Br, KO*t*Bu, THF, 23 °C, 2 h, followed by **2z**, −78 °C→23 °C, 20 h; 2) acryloyl chloride, NEt_3, CH_2Cl_2, 23 °C, 16 h; 3) Grubbs' 2nd generation catalyst, CH_2Cl_2, 45 °C, 24 h. b) 1) **2z**, MeI, NaH, THF, DMF, 0 °C, 2 h, then 23 °C, 12 h; 2) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 40 °C, 3 h; 3) BBr_3, CH_2Cl_2, 50 °C, 5 h. c) 1) **2z**, 3-bromopropene, K_2CO_3, acetone, 60 °C, 2 h; 2) Ph_3PCH_3Br, NaH, THF, 0 °C→23 °C, 2 h; 3) Grubbs' 1st generation catalyst, CH_2Cl_2, 23 °C, 2 h. d) 1) **2z**, 1-hexyne, *n*BuLi, THF, −78 °C, 1 h; 2) MnO_2, CH_2Cl_2, 23 °C, 1 h; K_2CO_3, acetone, 70 °C, 1 h. e) 1) **2z**, NH_4OAc, AcOH, $MeNO_2$, 135 °C, 3 h; 2) $NaBH_4$, 1,4-dioxane, EtOH, 0 °C, 1 h; 3) Bu_4NI, NEt_3, $PhI(OAc)_2$, MeCN, 35 °C, 30 min. f) 1) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 10 min, followed by NEt_3, **2z**, 0 °C, 30 min, then 23 °C, 1 h; 2) $PhB(OH)_2$, $Pd(OAc)_2$ (5.0 mol%), CuI (5.0 mol%), PPh_3, K_3PO_4, 1,4-dioxane, 100 °C, 24 h.

were easily converted into various valuable heterocycles. The high catalytic activity and unique chemoselectivity of the ruthenium(II) complexes in the challenging C–H oxygenation with weak aldehyde coordination illustrate the remarkable power of versatile and mild ruthenium(II) catalysis for the selective functionalization of unactivated C–H bonds.

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[13] Minor amounts of 3-chloro-4-methoxybenzaldehyde were also isolated as side products in all of the C–H oxygenations.

[14] Under otherwise identical reaction conditions, 1.25 mol% of the ruthenium catalyst delivered product **2a** in 43% yield.

[15] 4-Nitrobenzaldehyde has provided only unsatisfactory results thus far. Heteroaromatic aldehydes, such as pyridyl or thiophenyl derivatives, were not converted by the ruthenium catalyst, whereas an indole carbaldehyde reacted unselectively.

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