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COMMUNICATION

Ruthenium(II) oxidase catalysis for C–H alkenylations in biomass-derived γ-valerolactone

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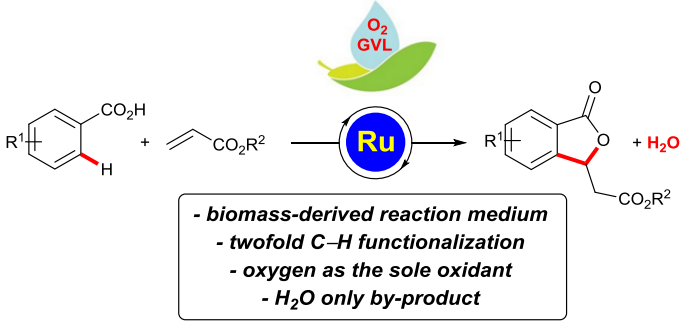
Ruthenium(II) biscarboxylate oxidase catalysis is a powerful tool for the assembly of functionalized arenes with oxygen as a green oxidant, but this strategy was thus far limited to its use in traditional organic solvents. Herein, we report on a green procedure for the ruthenium(II) biscarboxylate-catalysed C–H functionalisation in biomass-derived γ-valerolactone as the reaction medium. The oxidase catalysis was characterized by ample substrate scope and proceeded efficiently with oxygen as the sole oxidant. The overall green nature of this C–H-activation methodology is reflected by H_2O being the only by-product.

The transition metal-catalysed activation of otherwise inert C–H bonds has emerged as a powerful tool in molecular synthesis.[1] In contrast to conventional methods, the C–H functionalization approach avoids the installation and interconversion of functional groups, thereby improving the overall step- and atom-economy for a more sustainable access to organic molecules. In this context, ruthenium(II) biscarboxylate catalysis was identified as a particularly broadly applicable tool,[2] enabling *inter alia* C–H arylations,[3] C–H alkylations[4] or remote C–H functionalizations.[5] Notably, oxidative reaction control further enabled dehydrogenative twofold C–H functionalizations with alkenes or alkynes, but they usually required the use of stoichiometric amounts of silver(I) or copper(II) salts as the terminal oxidant.[6] However, within our program on sustainable C–H activation,[7] we very recently devised ruthenium(II) biscarboxylates for oxidase catalysis using oxygen as the sole oxidant in *n*-BuOH.[8] An additional green asset of this approach was represented by the formation of water as the only by-product.[8] Despite the indisputable progress, this approach was thus far limited to traditional, toxic organic solvents, compromising the overall green nature of our strategy. Moreover, undesired transesterifications and solvent oxidation occurred unfortunately as side reactions when using *n*-BuOH. During the past decade, major efforts have been made to identify novel approaches to convert biomass into raw materials and energy sources.[9] In order to obtain a broad range of chemicals in a cost-effective manner, several platform molecules have emerged, with γ-valerolactone (GVL) being a particularly attractive sustainable solvent.[10] In spite of the broad range of transformations that render γ-valerolactone a versatile precursor for bulk and fine chemicals,[10d, j, 11] it has unique properties that allow its use as a aprotic polar solvent,[10f-h] which was very recently exploited for palladium-catalysed direct functionalizations.[12] In stark contrast, we herein disclose the first ruthenium(II) oxidase C–H activation with molecular oxygen as the sole oxidant in green biomass-derived γ-valerolactone (Scheme 1). In this context, it is noteworthy that the organic reactants could largely be obtained from natural feedstocks, with the only by-product of the oxidase catalysis being environmentally-benign water. Furthermore, GVL is characterized by a higher flash point of 81 °C as compared to 35 °C for *n*-BuOH, leading to improved safety features.



Scheme 1: Ruthenium(II) oxidase catalysis in biomass-derived GVL.

We commenced our studies by probing various reaction conditions for the envisioned oxidative twofold C–H functionalisation of 2-

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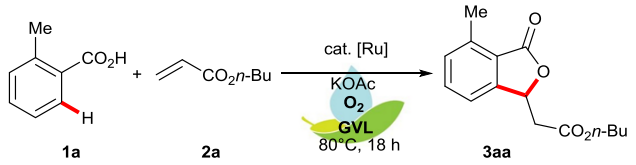
methylbenzoic acid (**1a**) with *n*-butyl acrylate (**2a**) (Table 1 and Table S-1 in the Electronic Supporting Information, ESI). A catalytic system consisting of $[RuCl_2(p\text{-cymene})]_2$ and KOAc in GVL (0.3M) (entry 1) under an ambient atmosphere of oxygen directly resulted in the effective formation of the desired product **3aa**. The dilution of pure GVL to a 2:1 GVL/H_2O mixture resulted in a somewhat decreased yield (entry 2). Reducing the amount of KOAc led to a lower catalytic efficacy (entry 3). The addition of equimolar amounts of HOAc gave a slightly better performance (entry 4), that could be further improved by increasing the substrate concentration. Control experiments confirmed the essential nature of the acetate additive and the ruthenium catalyst (Table S-1), while other typical ruthenium sources did not display any catalytic activity (entries 5-7).

Table 1: Optimisation of the ruthenium(II) oxidase **C–H** alkenylation of benzoic acid **1a**[a].

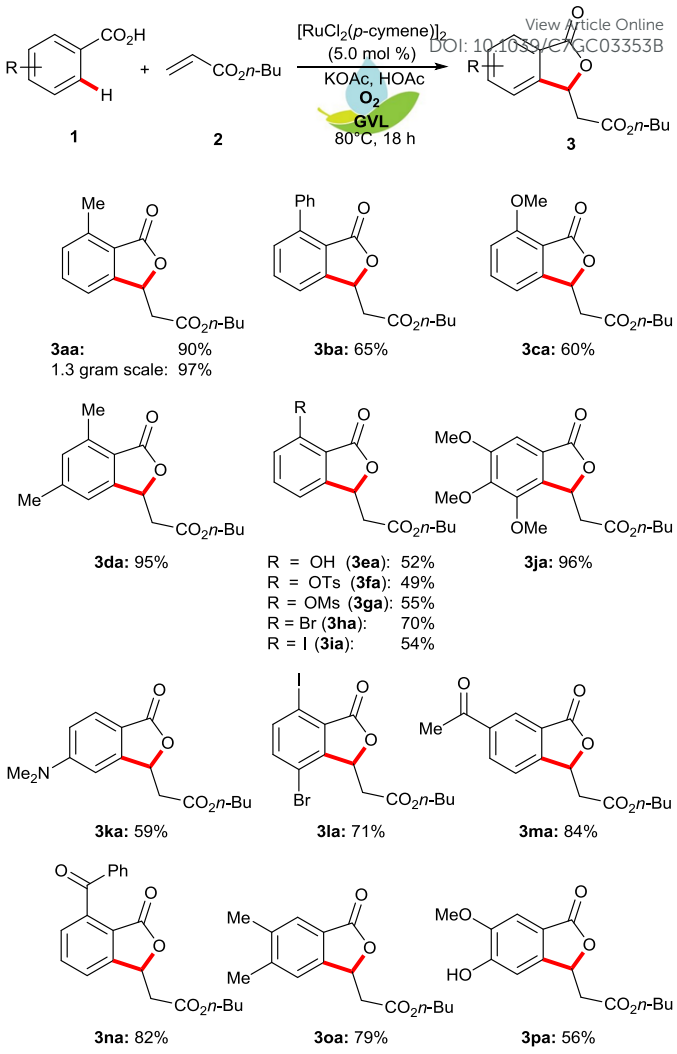


1a 2a 3aa

Entry	[Ru]	**1a** [M]	Yield [%][b]
1	$[RuCl_2(p\text{-cymene})]_2$	0.3	75
2[c]	$[RuCl_2(p\text{-cymene})]_2$	0.3	49
3[d]	$[RuCl_2(p\text{-cymene})]_2$	0.3	65
4[e]	$[RuCl_2(p\text{-cymene})]_2$	0.3	81
5	$[RuCl_2(cod)]_n$	1.0	traces
6	$[RuCl_2(p\text{-cymene})]_2$	1.0	88
7[e]	**$[RuCl_2(p\text{-cymene})]_2$**	**1.0**	**90**

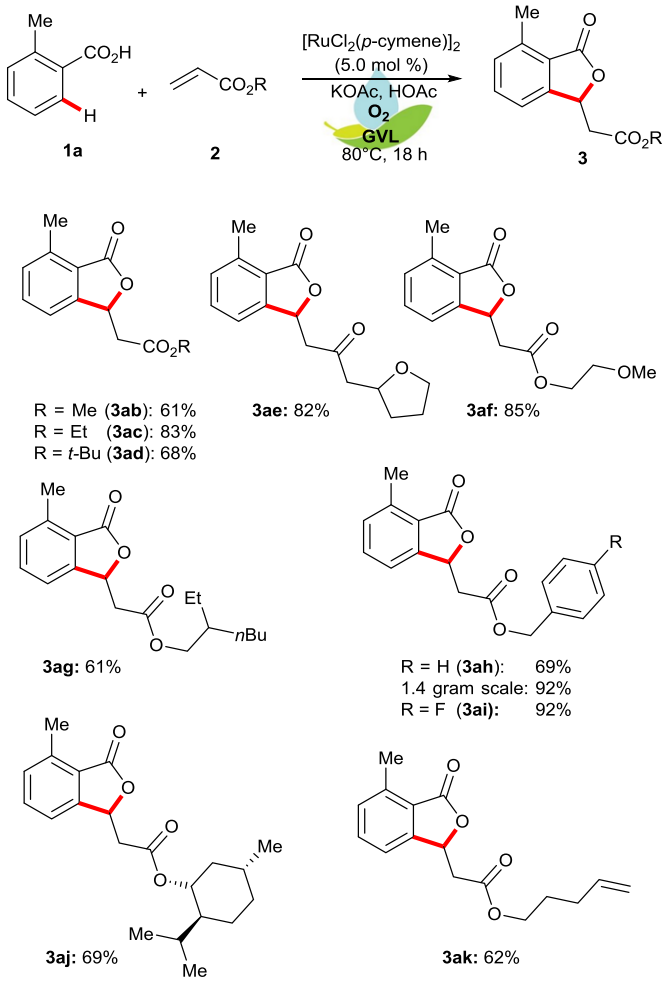
[a] Reaction conditions: **1a** (1.00 mmol), **2a** (1.50 mmol), [Ru] (10 mol %), KOAc (1.00 mmol), GVL (M), O_2 (1 atm), 80 °C, 18 h. [b] Isolated yield. [c] GVL (2.0 mL), H_2O (1.0 mL). [d] KOAc (0.5 mmol). [e] HOAc (1.0 mmol) added.

With the optimized reaction conditions in hand, we probed its versatility with differently decorated benzoic acids **1**. Thus, various functional groups, such as aryl, alkyl, ether, amino, bromo, iodo and ketone substituents, were well tolerated in the C–H activation, even in the *ortho*-position. These findings highlight the outstanding selectivity of the ruthenium(II) oxidase catalysis, while indicating its potential for further late-stage diversifications. The robustness of the oxidase C–H alkenylation was illustrated by the gram-scale preparation of phtalide **3aa** in an excellent isolated yield of 97%. The use of aprotic GVL as the reaction medium extended the scope of the C–H alkenylation to substrates bearing reactive tosylates and mesylates (**3fa** and **3ga**), again setting the stage for post-synthetic modifications towards bioactive compounds in medicinal chemistry and pharmaceutical industries. The positional selectivity of intramolecular competition experiments with *meta*-substituted arenes **1m**, **1o** and **1p** were dominated by steric interactions. Moreover, the naturally-occurring vanillic acid featuring the reactive hydroxyl group was chemo-selectively transformed to the phthalides **3la**.



Scheme 2: Ruthenium(II) oxidase catalysis with benzoic acids **1**.

Subsequently, we probed the robustness of the twofold C–H functionalization in GVL with a representative set of alkenes **2** (Scheme 2). Thus, the generality of the green oxidase catalysis was reflected by successfully providing access to various phthalides **3,** featuring among others a remote alkene in product **3ak**.



Scheme 3: Ruthenium(II)-catalysed oxidative annulation of alkenes **2**.

Since the aerobic C–H activation is exploiting oxygen as sole oxidant we explored the kinetic profile of the ruthenium(II) oxidase catalysis by its oxygen consumption, highlighting more than 80% conversion in less than 2 hours.

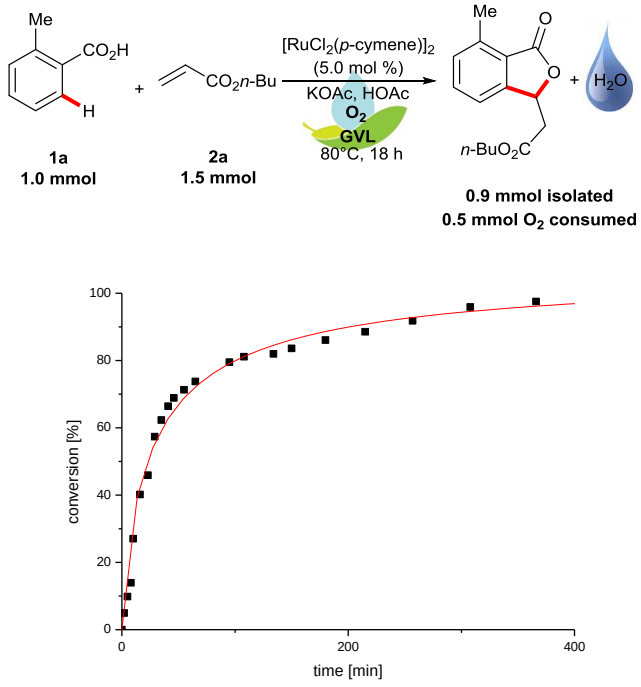
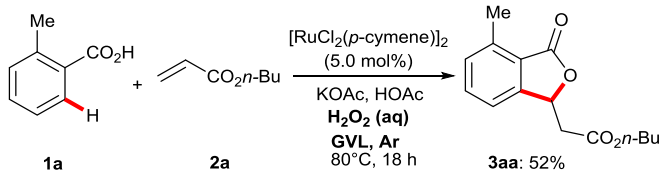


Figure 1: Oxygen consumption study.

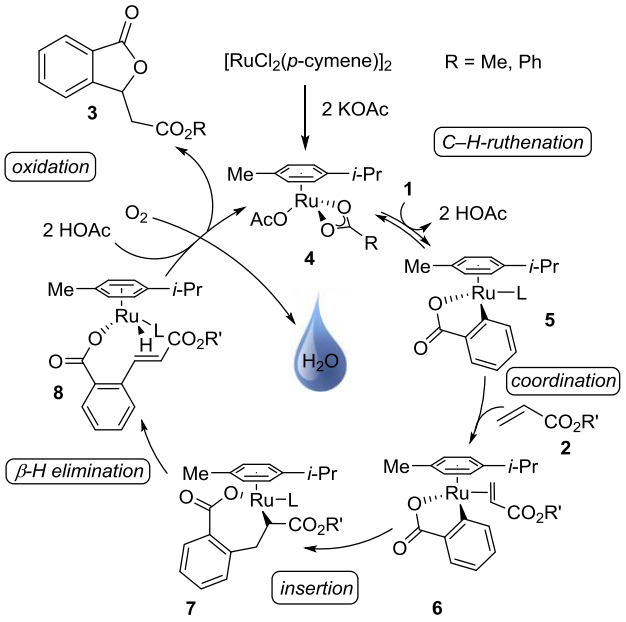
Because the use of molecular oxygen in the presence of flammable organic solvents can represent a potential safety hazard, we were pleased to find that the use of operationally-simple aqueous H_2O_2 could be similarly employed as the terminal oxidant (Scheme 4).



Scheme 4: Formation of 3aa with hydrogen peroxide as oxidant.

As to the reaction mechanism, a kinetic isotope effect (KIE) was not observed, when comparing the initial rates of transformations with substrates **1a** and [D_1]-**1a** (k_h/k_D = 1.0, see ESI), highlighting fast C–H activation in aprotic GVL. Based on our findings, we propose the plausible catalytic cycle depicted in Scheme 5. The *in-situ* generated ruthenium(II) biscarboxylate complex **4** undergoes facile base-assisted internal electrophilic-type substitution (BIES)[13] type C–H ruthenation of benzoic acid **1** to form the metallacycle **5.** The coordination of the alkene **2**, along with its insertion and a subsequent isomerisation, delivers complex **7**. Finally, the desired product **3** is obtained by β-hydride elimination and intramolecular oxa-Michael addition, while the catalytically active species **4** is

regenerated by a two electron oxidation step. Notably, the only stoichiometric by-product of the aerobic C–H alkenylation is H_2O.



Scheme 5: Proposed mechanistic cycle for the ruthenium oxidase.

Conclusion

In summary, we have reported on the first merger of oxidative ruthenium(II)-catalysed C–H functionalisation with a biomass-derived solvents. Thus, γ-valerolactone as green reaction medium set the stage for aerobic twofold C–H functionalizations between benzoic acids and alkenes. The oxidase ruthenium(II) biscarboxylate catalysis was characterized by excellent levels of positional and chemo-selectivity, fully tolerating reactive bromo, iodo or hydroxyl groups. The oxidative double C–H functionalizations employed molecular oxygen as the sole oxidant, generating environmentally-benign H_2O as the only stoichiometric by-product.

Acknowledgements

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