C–H Activation

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Ruthenium Oxidase Catalysis for Site-Selective C–H Alkenylations with Ambient O_2 as the Sole Oxidant

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In memory of Jonas Bang

Abstract: *Ruthenium(II) oxidase catalysis by direct dioxygen-coupled turnover enabled step-economical oxidative C–H alkenylation reactions at ambient pressure. Versatile ruthenium(II) biscarboxylate catalysts displayed ample substrate scope and proved applicable to weakly coordinating and removable directing groups. The twofold C–H functionalization strategy was characterized by exceedingly mild reaction conditions as well as excellent positional selectivity.*

Oxidative alkenylation by twofold C–H activation[1] arguably represents the most efficient and step-economical strategy for the assembly of selectively substituted olefins.[2] Based on pioneering studies by Fujiwara and Moritani,[3] tremendous progress has been made in metal-catalyzed cross-dehydrogenative olefinations, most notably in the area of palladium catalysis.[2,4] In contrast, versatile ruthenium(II) complexes[5] have only recently emerged as powerful catalysts for oxidative C–H functionalizations.[6] Despite these indisputable advances, ruthenium(II)-catalyzed oxidative alkenylations using chelation assistance have been thus far limited to the use of antibacterial copper(II) or expensive silver(I) salts as the oxidants.[6] Thereby, undesired metal waste is generated, which contradicts the sustainable nature of C–H activation technology. A notable elegant exception was developed by Milstein and co-workers, which indicated the potential of ruthenium catalysis.[7] Unfortunately, the catalyst was severely limited to rather harsh reaction conditions, such as high pressure reactions with CO at 8 atm and a reaction temperature of 180 °C. Moreover, mixtures of regioisomeric products which were difficult to separate were largely obtained when using substituted arenes.[7] As a consequence, there is a strong demand for ruthenium-catalyzed aerobic C–H functionalizations with positional selectivity under mild reaction conditions. In this context, Rueping and co-workers elegantly merged photoredox catalysis and C–H activation catalysts for simple and general aerobic alkenylations with a removable directing group.[8] In contrast, we have very recently identified the beneficial effect of carboxylates[9] for aerobic alkyne annulations.[10] Within our program on sustainable C–H functionalizations,[11] we herein report the first ruthenium(II)-catalyzed positional selective alkenylations with O_2 as the sole oxidant. Notable features of the versatile ruthenium oxidase catalysis by direct dioxygen-coupled turnover include: a) an unparalleled broad substrate scope in aerobic alkenylations, b) sustainable aerobic C–H activations that produce H_2O as the only by-product, c) exceedingly mild reaction conditions, and d) oxidative olefinations with weakly coordinating[12] or removable[13] directing groups (DG; Figure 1). As to the reaction mechanism, we provide

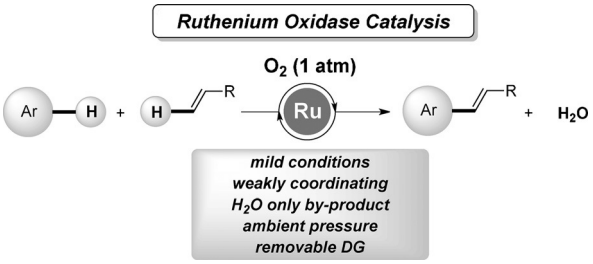

Figure 1. Ruthenium oxidase catalysis for C–H alkenylations.

strong support for a ruthenium oxidase catalysis manifold. It is also noteworthy that aerobic C–H alkenylations with more costly rhodium(III) complexes required strongly coordinating N-directing groups and thus far have not been accomplished with removable auxiliaries.[14]

We commenced our studies by exploring various reaction conditions for the aerobic C–H alkenylation of tosylbenzamide **1a** with alkene **2a**[15] under an atmosphere of ambient oxygen (Table 1; Table S1 in the Supporting Information). We were pleased to observe that the unprecedented ruthenium-(II)-catalyzed domino C–H alkenylation proved viable in the absence of copper(II) or silver(I) oxidants. The aerobic C–H functionalization proceeded most efficiently in the absence of a solvent (cf. entry 5 with entries 1–4). Among different acetate additives, KOAc was identified as being optimal (cf. entry 5 with entry 6). Furthermore, we verified that the ruthenium catalyst and the metal carboxylate were essential for the C–H activation process (entries 7 and 8).

Thereafter, we probed the versatility of the ruthenium(II) carboxylate catalyst in the aerobic assembly of isoindolinones

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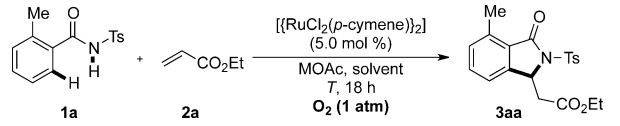
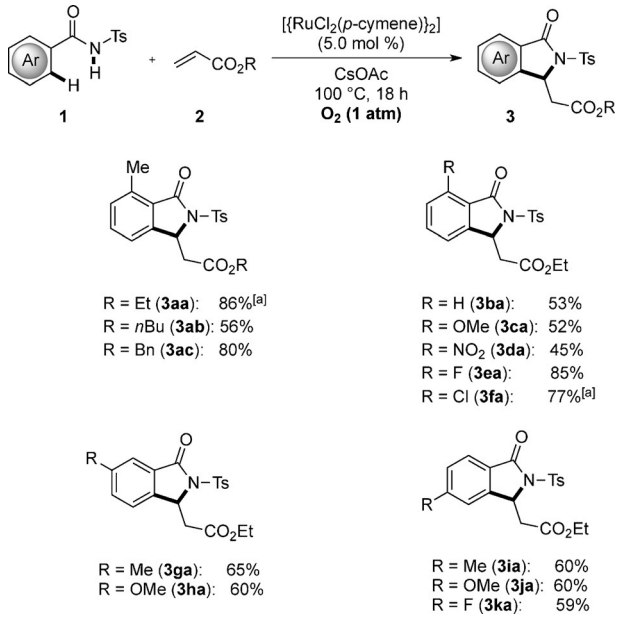
Table 1: Aerobic ruthenium(II)-catalyzed alkenylation with amide **1a**.[a]



Entry	Solvent	MOAc	*T* [°C]	Yield [%]
1	MeOH	CsOAc	80	30
2	DMF	CsOAc	80	20
3	DMF	CsOAc	100	26
4	DMF	KOAc	100	35
5	–	CsOAc	100	68[b]
6	–	KOAc	100	86[b]
7	–	CsOAc	100	–[c]
8	–	–	100	–

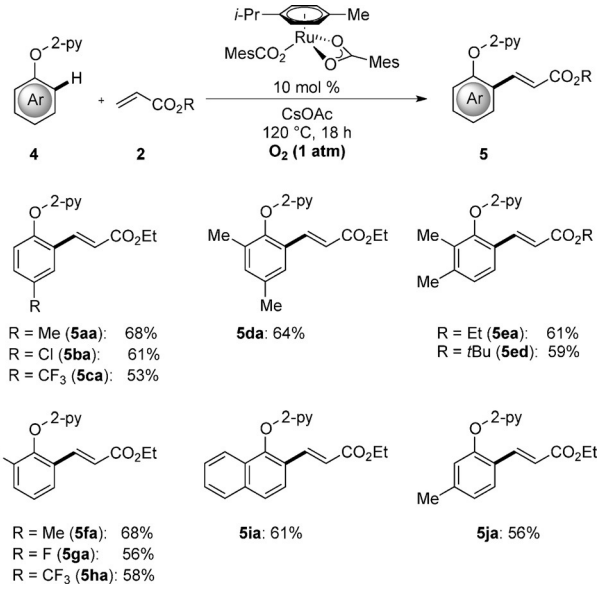
[a] Reactions conditions: **1a** (0.50 mmol), **2a** (1.5 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol%), MOAc (1.0 equiv), solvent (2.0 mL), 100°C, 18 h, O_2 (1 atm), yield of isolated product. [b] **2a** (2.5 mmol).[c] In the absence of [{$RuCl_2$(*p*-cymene)}$_2$]. DMF = dimethylformamide; *p*-cymene = 4-isopropyltoluene; Ts = tosyl.



Scheme 1. Aerobic ruthenium(II)-catalyzed assembly of isoindolinones **3**. [a] KOAc instead of CsOAc.

3 (Scheme 1). The oxidative cascade reaction occurred smoothly with *ortho*-substituted *N*-tosylamides **1a**–**1f** bearing synthetically useful functional groups, such as nitro or halo substituents. However, the ruthenium oxidase catalysis was not restricted to *ortho*-substituted amides **1**. Indeed, the C–H functionalization with *meta*- or *para*-substituted arenes **1g**–**1k** proceeded with excellent positional selectivity as well, with the latter transformations occurring at the less sterically hindered C–H bonds.

The versatile ruthenium(II) oxidase catalysis was not limited to the preparation of benzannulated heterocycles **3**. Indeed, the aerobic C–H functionalization also enabled aerobic alkenylations of phenol derivatives **4**[16] having a removable directing group (Scheme 2; Table S2). Thus, single-component ruthenium(II) biscarboxylates[17] could be



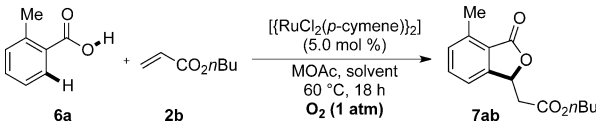
Scheme 2. Oxidase catalysis for C–H alkenylation with a removable DG. py = pyridyl; Mes = mesityl.

used to successfully catalyze reactions with excellent chemo- and positional selectivity.

Even challenging, weakly coordinating benzoic acids **6** proved to be suitable substrates.[18] Here, KOAc and CsOAc emerged as the ideal additives, which even allowed for aerobic C–H functionalization to occur under ambient air or at a reaction temperature of 25°C (Table 2; Table S3).

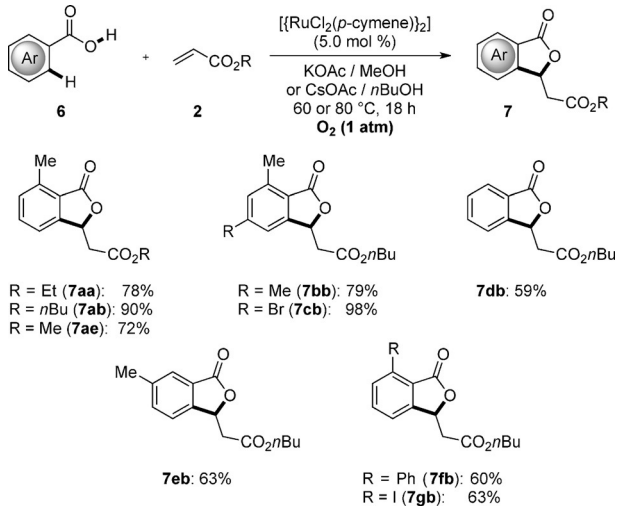
Thereby, differently functionalized benzoic acids **6** proved amenable for the step-economical synthesis of phthalides **7**[19] (Scheme 3)—key structural motifs in numerous bioactive natural products.[20] The outstanding chemoselectivity of the ruthenium(II) catalyst was reflected by the successful preparation of phthalides **7aa**–**7gb** displaying reactive bromo and

Table 2: Oxidase catalysis for C–H alkenylation of acid **6a**.[a]



Entry	Solvent	MOAc	*T* [°C]	Yield [%]
1	MeOH	CsOAc	60	82
2	MeOH	KOAc	60	88
3	MeOH	NaOAc	60	74
4	MeOH	–	60	–
5	EtOH	KOAc	60	78
6	*t*AmOH	KOAc	60	67
7	*n*BuOH	CsOAc	60	90
8	*n*BuOH	KOAc	80	90
9	*n*BuOH	KOAc	80	77[b]
10	MeOH	KOAc	37	82[c]
11	MeOH	KOAc	25	53[c]

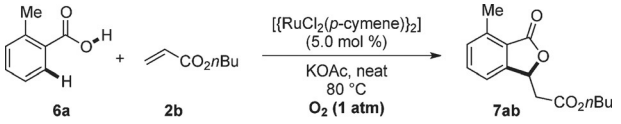
[a] Reactions conditions: **1a** (2.00 mmol), **2b** (1.0–1.1 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol%), MOAc (1.0 equiv), solvent (3.0 mL), 60°C, 18 h, O_2 (1 atm), yield of isolated product. [b] Under air (1 atm). [c] 2.5 days. *t*AmOH = 2-methyl-2-butanol.



Scheme 3. Aerobic ruthenium(II)-catalyzed synthesis of phthalides **7**.

iodo substituents among others, which should prove instrumental for further postsynthetic diversifications.

To probe the aerobic nature of the ruthenium(II)-catalyzed C–H activation process, we investigated the oxygen uptake during the course of the domino annulation (Figure 2). Our studies clearly showed that O_2 served as the



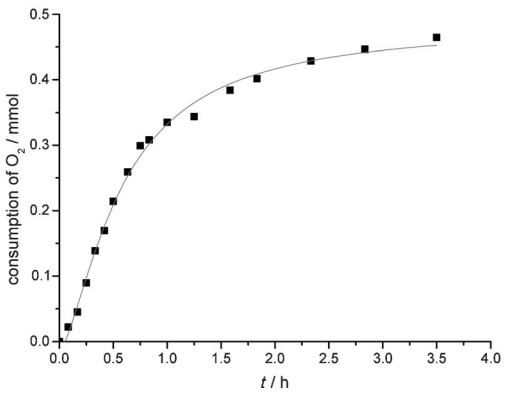
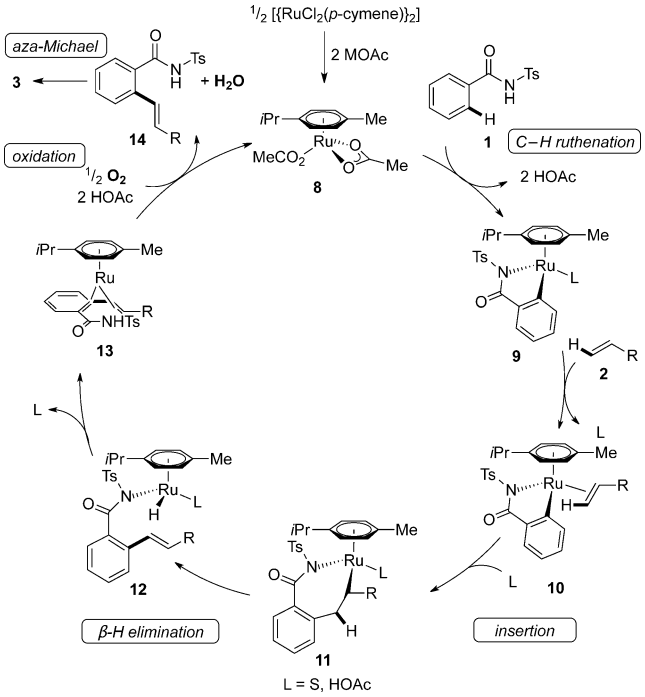


Figure 2. Oxygen consumption during ruthenium(II)-catalyzed C–H activation.

sole terminal oxidant in the C–H functionalization process with a direct dioxygen-coupled turnover. These findings also highlighted the efficacy of the oxidase catalysis, with 90% conversion of substrate **6a** in less than 4 hours. Additionally, mechanistic studies provided strong support for a rate-determining C–H ruthenation event with a kinetic isotope effect (KIE) of $k_H/k_D \approx 3.0$.[18]

Based on our mechanistic studies, we propose the aerobic C–H alkenylation to be initiated by an isohypsic, that is, redox-neutral, C–H metalation with ruthenium(II) biscarboxylate **8**, thereby furnishing cyclometalated intermediate **9** (Scheme 4). Thereafter, migratory alkene insertion delivers metallacyle **11**, which upon β-hydride elimination furnishes the ruthenium(II) hydrido complex **12**. Reductive elimination



Scheme 4. Proposed catalytic cycle for ruthenium oxidase C–H alkenylation. L = ligand.

subsequently leads to the ruthenium(0) intermediate **13**, which is oxidized by molecular oxygen at ambient pressure. The desired benzannulated product **3** is finally formed through an intramolecular aza-Michael reaction.

In summary, we have reported on ruthenium(II)-catalyzed oxidative alkenylation reactions with ambient oxygen as the sole oxidant under exceedingly mild[21] reaction conditions. The ruthenium oxidase catalysis occurred with ample substrate scope, and thus allowed for the olefination of arenes with weakly coordinating or removable directing groups through twofold C–H functionalizations. The aerobic C–H functionalization was characterized by user-friendly reaction conditions, even enabling oxidative olefinations even at ambient pressure at 25 °C. Finally, the green and sustainable nature of our oxidase catalysis approach was reflected by the production of water as the sole by-product.

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