C–H Activation Hot Paper

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Ruthenium(II)-Catalyzed C–H Activation/Alkyne Annulation by Weak Coordination with O_2 as the Sole Oxidant**

*Svenja Warratz, Christoph Kornhaaß, Ana Cajaraville, Benedikt Niepötter, Dietmar Stalke, and Lutz Ackermann**

Abstract: *Aerobic oxidative C–H functionalizations of weakly coordinating benzoic acids have been accomplished with versatile ruthenium(II) biscarboxylates under ambient oxygen or air. Mechanistic studies identified the key factors controlling the elementary step of the oxidation of the ruthenium(0) complex.*

Functionalizations of unreactive C–H bonds by annulations of substrates bearing C–C multiple bonds are powerful tools for the step-economical synthesis of bioactive heterocycles.[1] Recent years have witnessed the emergence of particularly versatile ruthenium(II) catalysts for oxidative alkyne annulations[2] by site-selective C–H functionalizations.[3,4] Despite these advances, all the ruthenium(II)-catalyzed alkyne annulations thus far required the use of additional oxidants, such as copper(II) or silver(I) salts, thereby leading to the formation of undesired stoichiometric metal-containing by-products. In contrast, molecular oxygen is significantly more attractive as a sacrificial oxidant, since it is inexpensive and leads to the formation of water as the only by-product.[5] Selected aerobic alkyne annulations have in the past few years been accomplished by palladium or rhodium catalysts by exploiting strongly coordinating nitrogen-containing directing groups, as elegantly developed by the research groups of Jiao[6] and Huang.[7–9] In contrast, ruthenium(II)-catalyzed oxidative C–H alkynylations with ambient oxygen have unfortunately proven elusive. Within our program on sustainable C–H activation,[10] we developed unprecedented ruthenium-catalyzed oxidative alkyne annulations with molecular oxygen as the cheapest sacrificial oxidant in the absence of any cooxidant (Figure 1). Herein, we present a user-friendly ruthenium(II) biscarboxylate catalyst that allowed for first aerobic alkyne annulations by weak oxygen-coordination,[11,12] along with mechanistic insights that highlight the key factors governing the crucial oxidation by molecular oxygen.

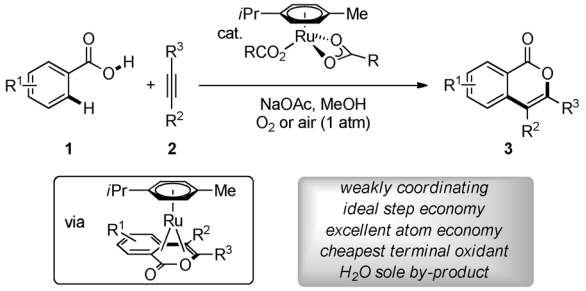

Figure 1. C–H activation of weakly coordinating benzoic acids **1** with O_2.

We commenced our studies by probing the oxidative C–H/O–H functionalization of 2-methylbenzoic acid (**1a**) with diphenylacetylene (**2a**) under an atmosphere of ambient oxygen (see Table 1 and Tables S1–S3 in the Supporting Information).

Methanol was identified as being the optimal solvent (entries 1–7). The desired synthesis of isocoumarin **3aa** also occurred under an atmosphere of ambient air, albeit with a somewhat reduced efficacy (entry 8). Interestingly, different ruthenium(II) precursors could be employed for efficient aerobic alkyne annulations (entries 9–11). It is noteworthy that the well-defined ruthenium(II) biscarboxylate complex[13,14] **4** delivered a comparable yield of the isocoumarin product **3aa** (entry 12).

We tested the versatility of the aerobic oxidative C–H/O–H functionalization under the optimized reaction conditions (Scheme 1). The in situ formed ruthenium(II) biscarboxylate complex proved to be broadly applicable and *ortho*-, *para*-, and *meta*-substituted benzoic acids **1** were efficiently converted into the corresponding isocoumarins **3**. The C–H functionalizations proceeded with excellent positional selectivity induced by the proximal carboxylic acid functionality. The robust ruthenium(II) catalyst was tolerant of valuable electrophilic functional groups, such as amino, bromo, and iodo substituents. We were also pleased to observe that heteroaromatic substrates, such as indoles, furans, and thiophenes, proved suitable for the alkyne annulation process (**3na**–**3pa**). Interestingly, the C–H ruthenation occurred site-

[*] M. Sc. S. Warratz,[+] Dr. C. Kornhaaß,[+] M. Sc. A. Cajaraville, Prof. Dr. L. Ackermann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de
Homepage: http://www.ackermann.chemie.uni-goettingen.de/
B. Niepötter, Prof. Dr. D. Stalke
Institut für Anorganische Chemie
Georg-August-Universität Göttingen
Tammannstrasse 4, 37077 Göttingen (Germany)
[+] These authors contributed equally to this work.

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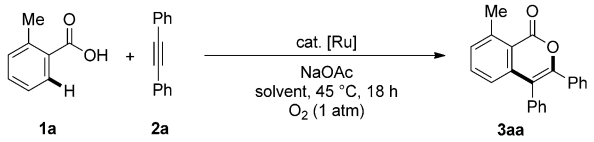
Table 1: Optimization of aerobic ruthenium-catalyzed alkyne annulation.[a]



1a 2a 3aa

Entry	[Ru]	Solvent	Yield[b] [%]
1	$[\{RuCl_2(p\text{-cymene})\}_2]$	*t*AmOH	<2[c]
2	$[\{RuCl_2(p\text{-cymene})\}_2]$	*i*PrOH	<2[c]
3	$[\{RuCl_2(p\text{-cymene})\}_2]$	EtOH	<2[c]
4	$[\{RuCl_2(p\text{-cymene})\}_2]$	MeCN	5[c]
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	PhMe	<2[c]
6	–	MeOH	–
7	*$[\{RuCl_2(p\text{-cymene})\}_2]$*	*MeOH*	*78*
8	$[\{RuCl_2(p\text{-cymene})\}_2]$	MeOH	49[d]
9	$[\{RuBr_2(p\text{-cymene})\}_2]$	MeOH	72
10	$[\{RuCl_2(\text{benzene})\}_2]$	MeOH	76
11	$RuCl_3\cdot(H_2O)_n$	MeOH	<2[c]
12	*$[\{Ru(OAc)_2(p\text{-cymene})\}_2]$ (4)*	*MeOH*	*83*

[a] Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), [Ru] (5.0 mol%), NaOAc (1.0 mmol), solvent (0.33 M), O_2 (1 atm), 45 °C, 18 h. [b] Yield of isolated product. [c] GC conversion with *n*-dodecane as the internal standard. [d] Under air (1 atm).

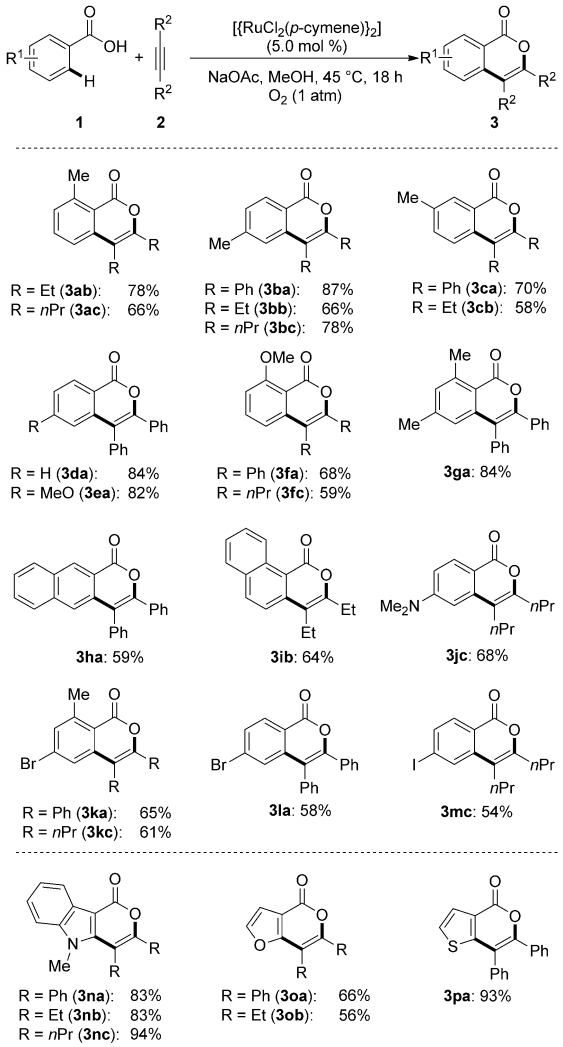
selectively at the kinetically more acidic C2-position of the heteroarenes **1n**–**1p**, which is indicative of a carboxylate-assisted concerted metalation-deprotonation/ambiphilic metal ligand activation (CMD/AMLA) type C–H ruthenation mechanism (see Scheme 6).[15]

Subsequently, we explored the regioselectivity of the C–H/O–H functionalization progress by employing unsymmetrically substituted alkynes **2** (Scheme 2). The ruthenium(II) catalyst delivered the desired products with excellent levels of regioselectivity,[16] generally placing the aliphatic substituent in all cases distal to the oxygen heteroatom. Thereby, our approach provided step-economical access to isocoumarins **3fg** and **3qg** derived from the bioactive[17] natural products thunberginols A and B.[18]

Given the importance of ruthenium-catalyzed aerobic oxidation beyond C–H activation, we became intrigued by the mechanism of the ruthenium(II)-catalyzed aerobic alkyne annulation. To this end, we determined the kinetic isotope effect to be $k_H/k_D \approx 4.5$, which suggests the C–H ruthenation to be the rate-determining step (Scheme 3 and Scheme S1 in the Supporting Information).

Subsequently, we tested the stoichiometric reaction of alkynes **2** with cyclometalated[19] complexes **5** in the absence of an oxidant. Intriguingly, these transformations directly delivered the ruthenium(0) sandwich complexes **6** with the isocoumarins **3** as neutral ligands (Scheme 4). The direct formation of ruthenium(0) complexes **6** was observed for all cyclometalated substrates **5** and alkynes **2**. These observations are a strong testament to a facile reductive elimination of the corresponding seven-membered ruthena(II)cycle. The structure of the ruthenium(0) complex **6f** was unambiguously verified by X-ray single crystal diffraction analysis (Figure 2).

Thereafter, the key aerobic reoxidation of the ruthenium(0) sandwich complexes **6** was probed in stoichiometric



Scheme 1. Scope of the aerobic ruthenium(II)-catalyzed alkyne annulation.

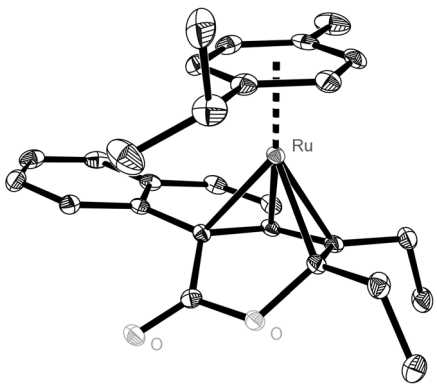
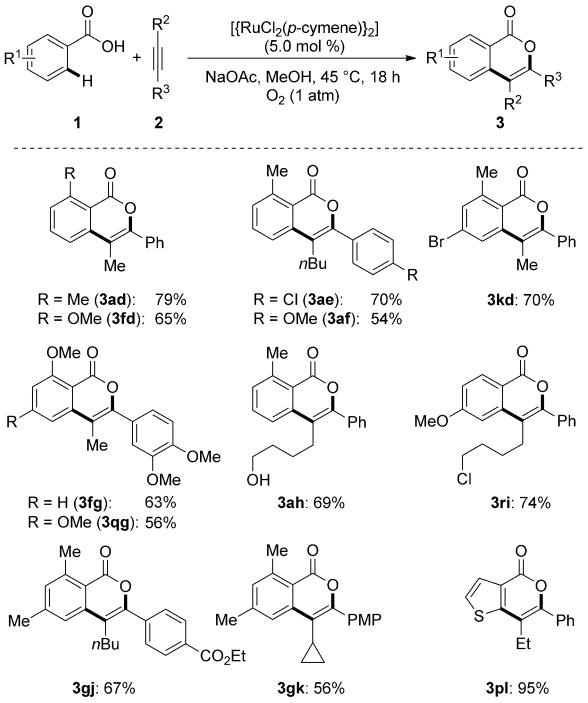
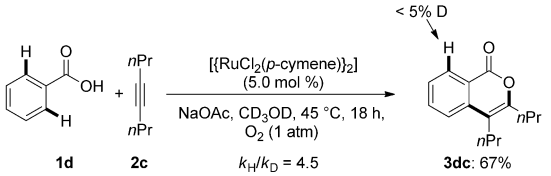


Figure 2. Molecular structure of complex **6f**. H atoms are omitted for clarity. Anisotropic displacement parameters are depicted at the 50% probability level.

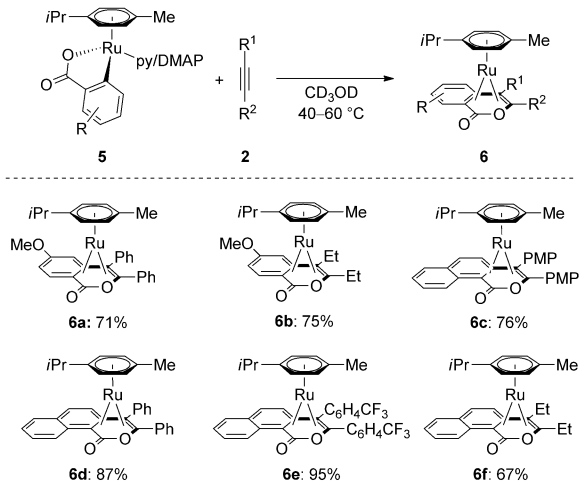
experiments (Scheme 5). Notably, acetate additives, such as $Cu(OAc)_2\cdot H_2O$ or NaOAc, failed to facilitate the ruthenium(0) oxidation. In contrast, acetic acid set the stage for an



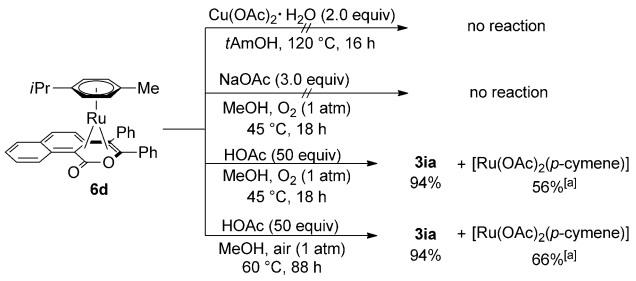
Scheme 2. Aerobic ruthenium(II)-catalyzed C–H activation with unsymmetrical alkynes **2**.



Scheme 3. Studies highlighting the rate-determining C–H ruthenation.



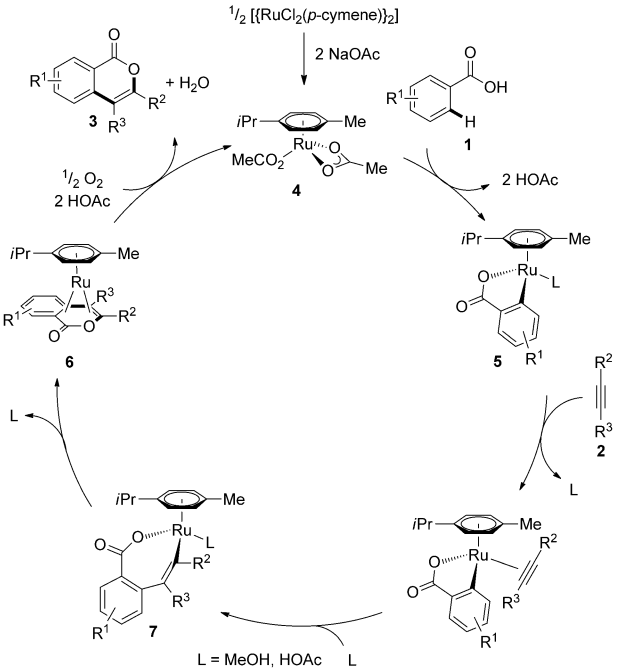
Scheme 4. Transformation of ruthena(II)cycles **5** with alkynes **2** as monitored by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard.



Scheme 5. Oxidation of ruthenium(0) complexes **6**. [a] Determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard.

efficient generation of the ruthenium(II) complex [Ru(OAc)$_2$(*p*-cymene)] (**4**), which at the same time led to the liberation of the isocoumarin **3ia**. Interestingly, the ruthenium(0) oxidation could also be achieved with air as the sacrificial oxidant, although at a slightly elevated temperature of 60 °C.

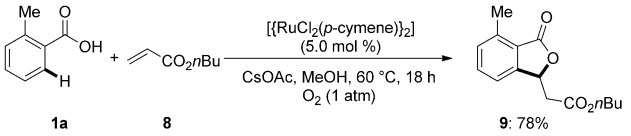
Based on our mechanistic studies we propose a plausible catalytic cycle to involve a rate-determining, isohypsic cycloruthenation with the ruthenium(II) bisacetate complex **4** (Scheme 6). Thereby, ruthena(II)cycle **5** is generated, along with two equivalents of acetic acid. Thereafter, coordination and migratory insertion of an alkyne furnishes the seven-membered ruthena(II)cycle **7**.[20] Intermediate **7** rapidly undergoes reductive elimination to yield the ruthenium(0) sandwich complex **6**, which in the key step is reoxidized by molecular oxygen. This reoxidation of ruthenium(0) requires the initially formed acetic acid and sets free the isocoumarin **3**. We propose the ruthenium(0) reoxidation to occur by



Scheme 6. Proposed catalytic cycle for alkyne annulation with oxygen.

a single-electron transfer process to produce a peroxoruthenium species which further reacts to the catalytically active ruthenium(II) bisacetate.[21] At the same time, H_2O is formed as the sole stoichiometric by-product.

Finally, we were pleased to find that ruthenium(II) biscarboxylates were not limited to aerobic annulations of alkynes **2**. Indeed, the C–H functionalization with alkene **8** was also accomplished at a slightly elevated reaction temperature in a site-selective fashion (Scheme 7).



Scheme 7. Aerobic ruthenium(II)-catalyzed annulation of alkene **8**.

In summary, we have reported the unprecedented oxidative ruthenium-catalyzed alkyne annulation by C–H functionalization with molecular oxygen as the sole oxidant. Thus, ruthenium(II) biscarboxylates set the stage for the expedient synthesis of isocoumarins from weakly coordinating benzoic acids in the absence of cooxidants. The C–H/O–H functionalization process proceeded with excellent levels of chemo-, site-, and regioselectivities under mild reaction conditions, and generated water as the only by-product. Mechanistic studies unraveled the key importance of acetic acid for the crucial reoxidation of ruthenium(0) by molecular oxygen, which also set the stage for efficient aerobic alkene annulations.

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Keywords: benzoic acids · C–H activation · dioxygen · oxidation · ruthenium

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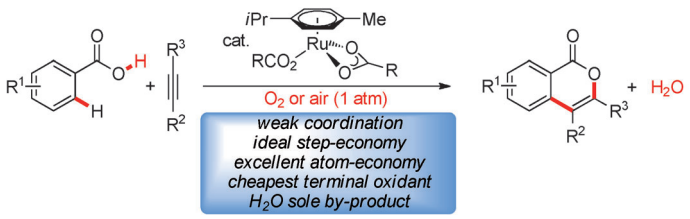
Communications

C–H Activation

S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke, L. Ackermann* _____ ■■■■–■■■■

Ruthenium(II)-Catalyzed C–H Activation/Alkyne Annulation by Weak Coordination with O_2 as the Sole Oxidant



Air and water: Ruthenium(II) biscarboxylates allow for the annulation of alkynes and alkenes by oxidative C–H functionalizations with molecular oxygen as the sole oxidant. The C–H/O–H functionalization process occurs with excellent selectivities under mild reaction conditions, with water produced as the only by-product.

