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Electrochemical ruthenium-catalyzed alkyne annulations by C–H/Het–H activation of aryl carbamates or phenols in protic media†

Ruhuai Mei, Julian Koeller and Lutz Ackermann *

Electrooxidative *peri*-C–H activation was accomplished by versatile ruthenium(II) catalysis in terms of C–H/N–H and C–H/O–H functionalization. Thus, alkyne annulations proved viable with ample scope by organometallic C–H activation. The sustainable electrocatalysis exploited electricity, thereby avoiding the use of toxic transition metals as sacrificial oxidants. The robust ruthenium(II)-electrocatalysis was operative in a protic alcohol/H_2O reaction medium with excellent levels of position-, regio- and chemo-selectivity.

Transition metal-catalyzed oxidative C–H activation[1] has been recognized as a powerful tool for the assembly of π-conjugated heterocycles, with major potential for molecular syntheses and material sciences.[2] Despite of considerable progress, these oxidative C–H functionalizations heavily rely on stoichiometric amounts of expensive and toxic metal salts as the sacrificial oxidants.[3] Electrosynthesis[4] has emerged as an increasingly viable platform for sustainable transformations, which enables the use of inexpensive electricity as the terminal oxidant.[5] In this context, major advances were achieved, exploiting transition-metals based on *inter alia* palladium,[6] cobalt,[7] ruthenium,[8] rhodium,[9] copper,[10] or iridium.[11]

Recently, we have introduced a versatile ruthenium[12] catalyst for oxidative C–H/O–H annulation of alkynes[13] by 1-naphthols to access fused pyran derivatives.[14] Despite considerable experimentation, these transformations were restricted to the use of anti-bacterial copper(II) oxidants. Within our program on sustainable C–H activation,[15] we have now developed the first electrochemical, organometallic *peri* C–H activation with synthetically meaningful arylcarbamates,[16] on which we report herein (Fig. 1). Notable features of our finding include (a) the first electrooxidative ruthenium-catalysed *peri* C–H activation, (b) C–H/N–H annulation by electrooxidative ruthenium catalysis, (c) weakly coordinating[17] naphthol for C–H/O–H alkyne annulations with electricity as the terminal oxidant, and (d) mechanistic insights into electrochemical *peri* C–H activation by experiments. It is furthermore noteworthy that our electrooxidative strategy also set the stage for the first ruthenium-catalyzed C–H/N–H activation/alkyne annulation of naphthylcarbamates.

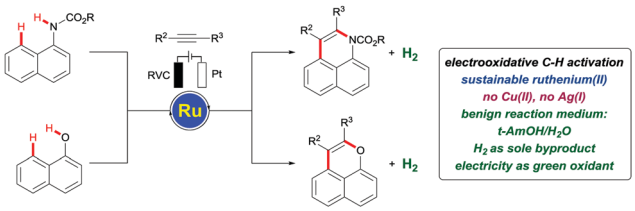

Fig. 1 Electrochemical C–H/Het–H activation with alkynes.

At the outset of our studies, we tested various reaction conditions for the envisioned electrooxidative annulation of alkyne **2a** by easily-accessible ethyl naphthalen-1-ylcarbamate (**1a**) (Table 1 and Table S-1 in the ESI†).[18] Among a set of representative solvents, DMF and *t*-AmOH furnished promising results (entries 1 and 2), while a solvent mixture of *t*-AmOH and H_2O,[19] along with KOAc as the additive, proved to be ideal (entries 3–6). The catalytic efficacy could be further improved when the electrolysis was conducted at a constant current regime of 1.5 mA (entries 7–9). Control experiments demonstrated the outstanding performance of the ruthenium(II) carboxylates (entries 9–11), while typically used rhodium(III) catalysts fell short in delivering the desired product **3aa** (entry 12).

With the optimized ruthenium electrocatalysis being established, we explored its versatility with a set of representative internal alkynes (Scheme 1). Thus, the broadly applicable ruthenium(II) catalyst enabled the efficient conversion of diaryl- and dialkyl-substituted alkynes **2a–2i**. The robust ruthenium-electrocatalysis displayed a remarkable tolerance of valuable functional groups, such as ester, fluoro, chloro, or bromo substituents, setting the stage for further late-stage diversifications. Unsymmetrical alkyne **2j** delivered the desired product **3aj** with high levels of regio-control, placing the aromatic moiety in proximity to the nitrogen heteroatom.

Institute for Organic and Biomolecular Chemistry, Georg-August-Universität Göttingen, Tammannstr. 2, 37077 Göttingen, Germany.
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de

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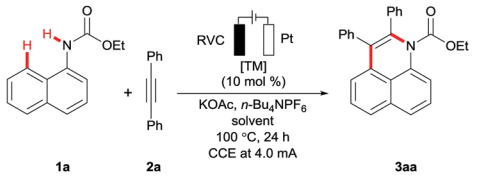
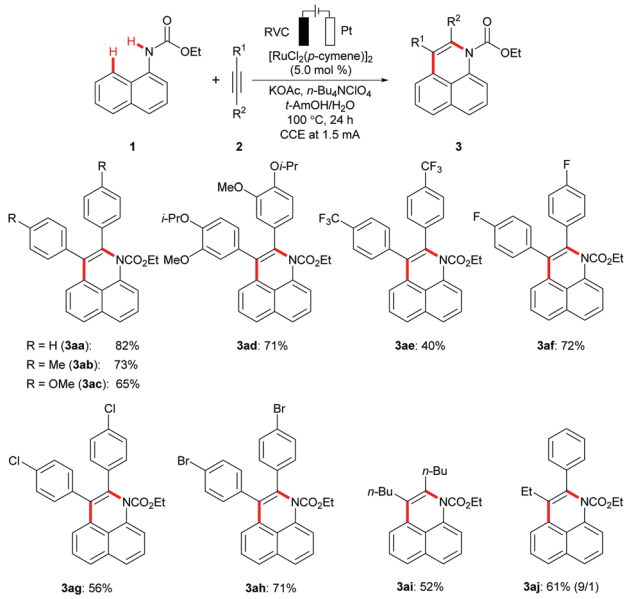
Table 1 Establishing the electrochemical C–H/N–H activation[a]



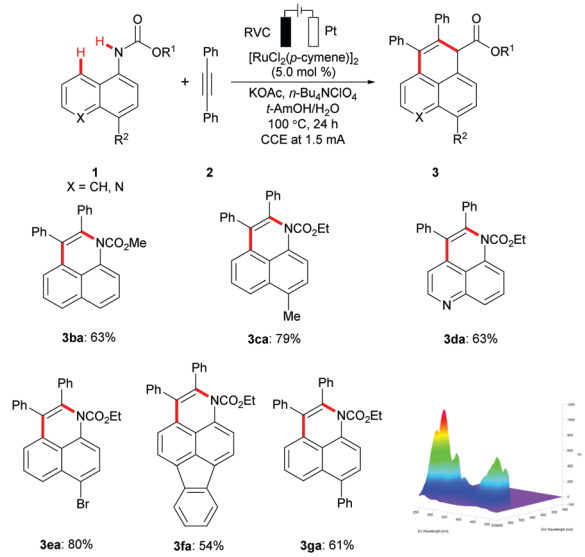
Entry	[TM]	Solvent	Yield [%]
1	$[RuCl_2(p\text{-cymene})]_2$	DMF	35
2	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH	51
3	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH/H_2O (3/1)	61
4	$[RuCl_2(p\text{-cymene})]_2$	DMF/H_2O (3/1)	28
5	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH/H_2O (3/1)	57[b]
6	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH/H_2O (3/1)	65[c]
7	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH/H_2O (3/1)	36[c,d]
8	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH/H_2O (3/1)	77[c,e]
9	**$[RuCl_2(p\text{-cymene})]_2$**	***t*-AmOH/H_2O (3/1)**	**82**[c,f]
10	$[RuCl_2(p\text{-cymene})]_2$	*t*-AmOH/H_2O (3/1)	31[c,g]
11	—	*t*-AmOH/H_2O (3/1)	<5[c,f]
12	$[Cp^*RhCl_2]_2$	*t*-AmOH	<5

[a] General reaction conditions: **1a** (0.60 mmol), **2a** (0.30 mmol), [TM] (10 mol %), KOAc (0.60 mmol), *n*-Bu_4NPF_6 (0.18 mmol), solvent (4.0 mL), 100 °C, 16 h, under N_2, constant current electrolysis (CCE) at 4.0 mA, undivided cell, RVC anode, Pt-plate cathode. Isolated yields. [b] NaOPiv (0.60 mmol) instead of KOAc. [c] *n*-Bu_4NClO_4 (0.18 mmol) instead of *n*-Bu_4NPF_6. [d] 10 mA, 2.5 h. [e] 2.0 mA, 16 h. [f] 1.5 mA, 24 h. [g] Without current, 24 h.



Scheme 1 Electrochemical C–H/N–H annulation of alkynes **2**.

Subsequently, a variety of arylcarbamates **1** were probed, highlighting an outstanding selectivity for the *peri* C–H activation to deliver benzoquinoline derivatives **3** (Scheme 2). Ethyl naphthalen-1-ylcarbamates **1** bearing either electron-withdrawing or electron-donating groups on the naphthyl ring provided the corresponding benzoquinolines **3** with high efficacy. It is worth noting that the ruthenium(II) electrocatalysis was likewise applicable to heterocyclic substrate ethyl quinolin-5-ylcarbamate **1d**, selectively furnishing the annulated product **3da**. Likewise,

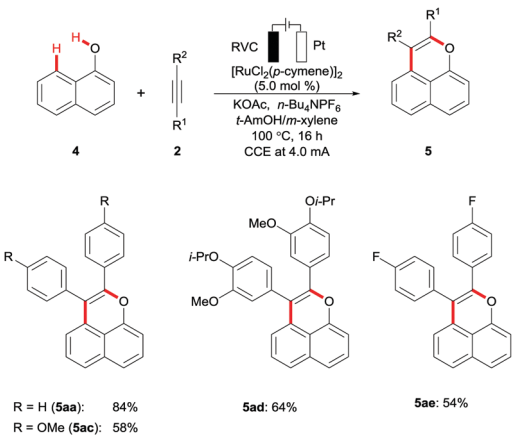


Scheme 2 Electrochemical C–H/N–H activation with amides **2**.

the extended aromatic substrate fluoranthen-3-ylcarbamate **1f** was smoothly converted to give the π-conjugated polyheterocycles **3fa**, featuring unique fluorescence emission.

The ruthenium(II) electrocatalysis was not limited to C–H/N–H activation with arylcarbamates **1**. Indeed, highly effective annulations of alkynes **2** proved to be viable with the weakly coordinating[17] naphthol derivatives **4** (Scheme 3, and Table S-2 in the ESI†).[18] Thus, a series of fluorescent pyrans were accessed in a step-economical fashion *via* the chemo-selective C–H/O–H functionalization, featuring electricity as the sacrificial oxidant.

Given the unique site- and regio-selectivity of the electrochemical ruthenium(II) catalysis, we became interested in its modus operandi. To this end, a catalytic C–H transformation in the presence of D_2O employing an excess of substrate **1a** resulted in a significant H/D exchange in the *peri*-position of the recovered starting material [D_1]-**1a** (Scheme 4a). This observation provided strong evidence for a reversible, organometallic C–H ruthenation step. In good agreement with this finding, a kinetic isotope effect (KIE) was not observed, when comparing



Scheme 3 Electrochemical C–H/O–H activation with naphtholes **4**.

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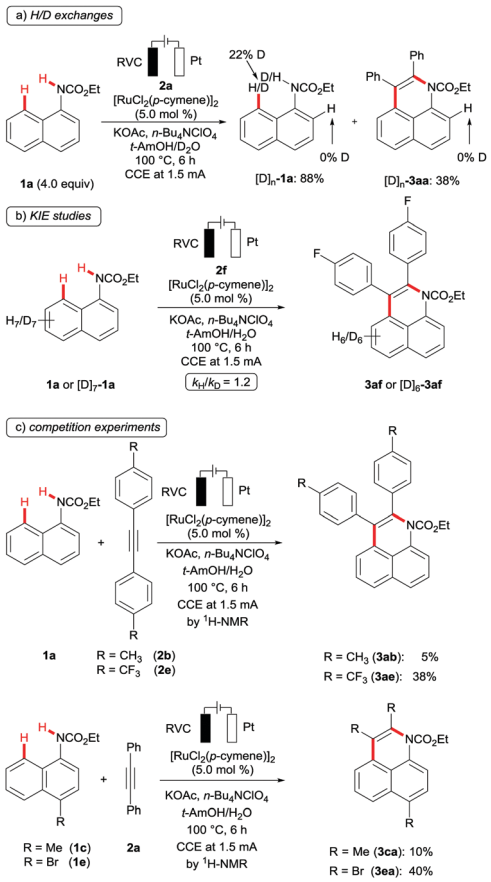
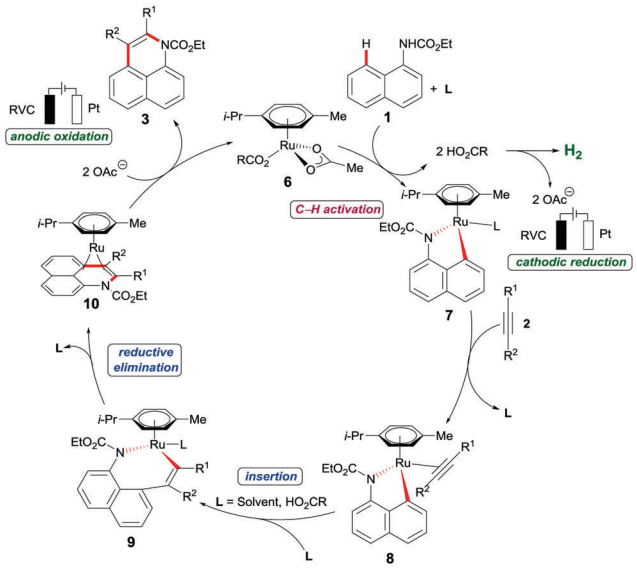


Scheme 4 Summary of key mechanistic findings.

the initial rates of transformations with substrates **1a** and [D_7]-**1a** (Scheme 4b). Furthermore, we performed intermolecular competition experiments between differently substituted arylcarbamates **1** and alkynes **2**, which revealed electron-deficient alkynes and arylcarbamates to be preferentially converted (Schemes 4c and d).



Scheme 5 Proposed catalytic cycle.

Based on our mechanistic studies, we propose a plausible catalytic cycle to commence by a facile organometallic C–H activation (Scheme 5). Thereby, ruthena(II)cycle **7** is generated, along with two equivalents of carboxylic acid. Thereafter, migratory alkyne insertion furnishes the seven-membered ruthena(II)cycle **9**, which rapidly undergoes reductive elimination to deliver the ruthenium(0) sandwich complex **10**. The key reoxidation of the thus-formed ruthenium(0) complex **10** is finally accomplished by anodic oxidation, while cathodic reduction generates molecular hydrogen as the sole stoichiometric byproduct.

In summary, we have reported on the first electrocatalytic organometallic C–H activation with aromatic carbamates and phenols. Hence, a versatile ruthenium(II) carboxylate catalyst enabled electrooxidative C–H/N–H and C–H/O–H activation/alkyne annulations with ample scope. The C–H activation employed electricity as the sacrificial oxidant, which avoids the use of toxic metals as terminal oxidants, generating molecular hydrogen as the only byproduct. Mechanistic studies provided strong support for an organometallic C–H ruthenation, along with an efficient electro-reoxidation of the key ruthenium(0) intermediate by environmentally-benign electricity that is amenable for renewable forms of energy. The electrochemical C–H/Het–H activation was operative in protic aqueous reaction media.

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Conflicts of interest

There are no conflicts to declare.

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