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Ruthenaelectro-catalyzed C–H acyloxylation for late-stage tyrosine and oligopeptide diversification†

Xiaoyan Hou,‡[a] Nikolaos Kaplaneris,‡[a] Binbin Yuan,[a] Johanna Frey,[a] Tsuyoshi Ohyama,[a] Antonis M. Messinis[a] and Lutz Ackermann*[ab]

Ruthenaelectro(II/IV)-catalyzed intermolecular C–H acyloxylations of phenols have been developed by guidance of experimental, CV and computational insights. The use of electricity bypassed the need for stoichiometric chemical oxidants. The sustainable electrocatalysis strategy was characterized by ample scope, and its unique robustness enabled the late-stage C–H diversification of tyrosine-derived peptides.

Introduction

During the last decade C–H activation has been recognised as a transformative platform in molecular syntheses[1] with enabling applications to *inter alia* natural products syntheses,[2] material sciences[3] and medicinal chemistry.[4] Among the transition metals that have been utilized for direct C–H activations ruthenium complexes,[5] due to their robustness and cost-effectiveness, offer an appealing opportunity for sustainable molecular modifications. Due to the widespread occurrence of phenols in a plethora of bioactive compounds related to crop protection,[6] molecular syntheses[7] and drug development,[8] phenol derivatives are uniquely appealing target motifs.[9] As a consequence, direct C–H functionalizations on phenol derivatives represent a desirable approach towards value-added compounds.[10] Recently, C–H activation has been identified as a powerful tool for late-stage diversification of complex biomolecules.[11,12] C–H acyloxylation has attracted major attention in recent years.[13] Over the past decade, tremendous efforts have been made to promote C–H acyloxylations, utilizing palladium,[14] rhodium[15] and ruthenium complexes,[16] among others.[17] Despite this indisputable progress, stoichiometric amounts of chemical oxidants are generally required, leading to undesired waste-products, jeopardizing the overall atom-economical nature of the C–H activation approach.

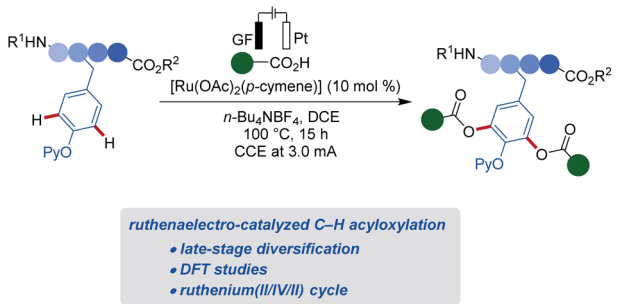

Fig. 1 Electrocatalytic C–H acyloxylation of tyrosine containing peptides.

Electroorganic synthesis has surfaced as an increasingly viable tool for sustainable syntheses.[18] In this context, the merger of C–H activation and electrooxidation was recently recognized as a particularly powerful tool for molecular catalysis, avoiding stoichiometric amounts of chemical oxidants.[19]

Despite of indisputable advances in electrocatalysis,[20] late-stage amino acid or peptide diversifications are unprecedented. In stark contrast, we, herein, disclosed the first electrochemical selective oxygenations of sensitive phenols for late-stage tyrosine diversification (Fig. 1). Salient features of our findings include: (a) resource-economical C–H acyloxylations with electricity as sustainable oxidant *in lieu* of stoichiometric chemical oxidants; (b) effective ruthenium catalysis in an user-friendly undivided cell setup; (c) mechanistic insights into the electrooxidative ruthenium catalysis *via* the isolation of key intermediates and (d) bioorthogonal C–H acyloxylation for late-stage diversifications of tyrosine-derived peptides.

Results and discussion

We initiated our studies by exploring reaction conditions for the envisioned electrochemical C–H acyloxylations of phenol **1a** with a removable pyridine[21] in an undivided cell setup equipped

[a]*Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstraße 2, 37077 Göttingen, Germany. E-mail: Lutz.Ackermann@chemie.uni-goettingen.de*

[b]*German Center for Cardiovascular Research (DZHK), Potsdamer Straße 58, 10785 Berlin, Germany*

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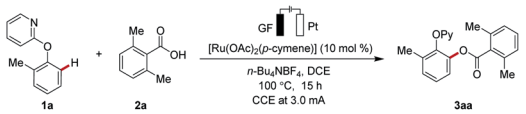
‡ These authors contributed equally to this work.

Table 1 Optimisation of ruthenaelectro-catalyzed C–H acyloxylation[a]



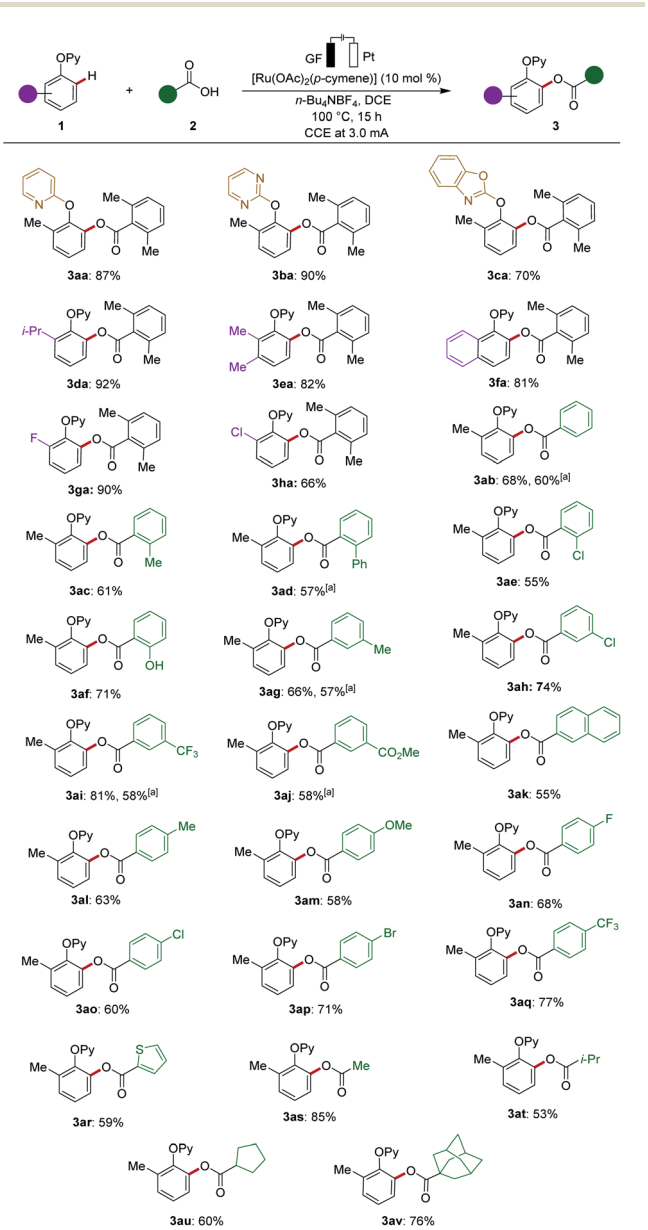
Entry	Deviation from standard conditions	Yield
1	No change	87%
2	TFE as solvent, 80 °C	36%
3	TFE as solvent	65%
4	EtOH as solvent	—
5	*t*-AmOH/H_2O (3/1) as solvent	—
6	$[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in place of [Ru]	78%
7	$[Ru_2(OAc)_4Cl]$ (5 mol%) in place of [Ru]	86%
8	$[RuCl_3\cdot 3H_2O]$ in place of [Ru]	66%
9	$[RhCl_3\cdot 3H_2O]$ in place of [Ru]	—
10	$[Cp^*RhCl_2]_2$ (5 mol%) in place of [Ru]	15%
11	$[Cp^*IrCl_2]_2$ (5 mol%) in place of [Ru]	<5%
12	$[Cp^*CoI_2(CO)]$ in place of [Ru]	—
13	Without [Ru]	—
14	No electricity	—

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.40 mmol), $[Ru(OAc)_2(p\text{-cymene})]$ (10 mol%), *n*-Bu_4NBF_4 (0.25 mmol), DCE (4.0 mL), 100 °C 15 h, undivided cell, GF anode, Pt cathode, under air, constant current = 3.0 mA. Py = pyridyl, TFE = 2,2,2-trifluoroethanol, DCE = 1,2-dichloroethane, [Ru] = $[Ru(OAc)_2(p\text{-cymene})]$.

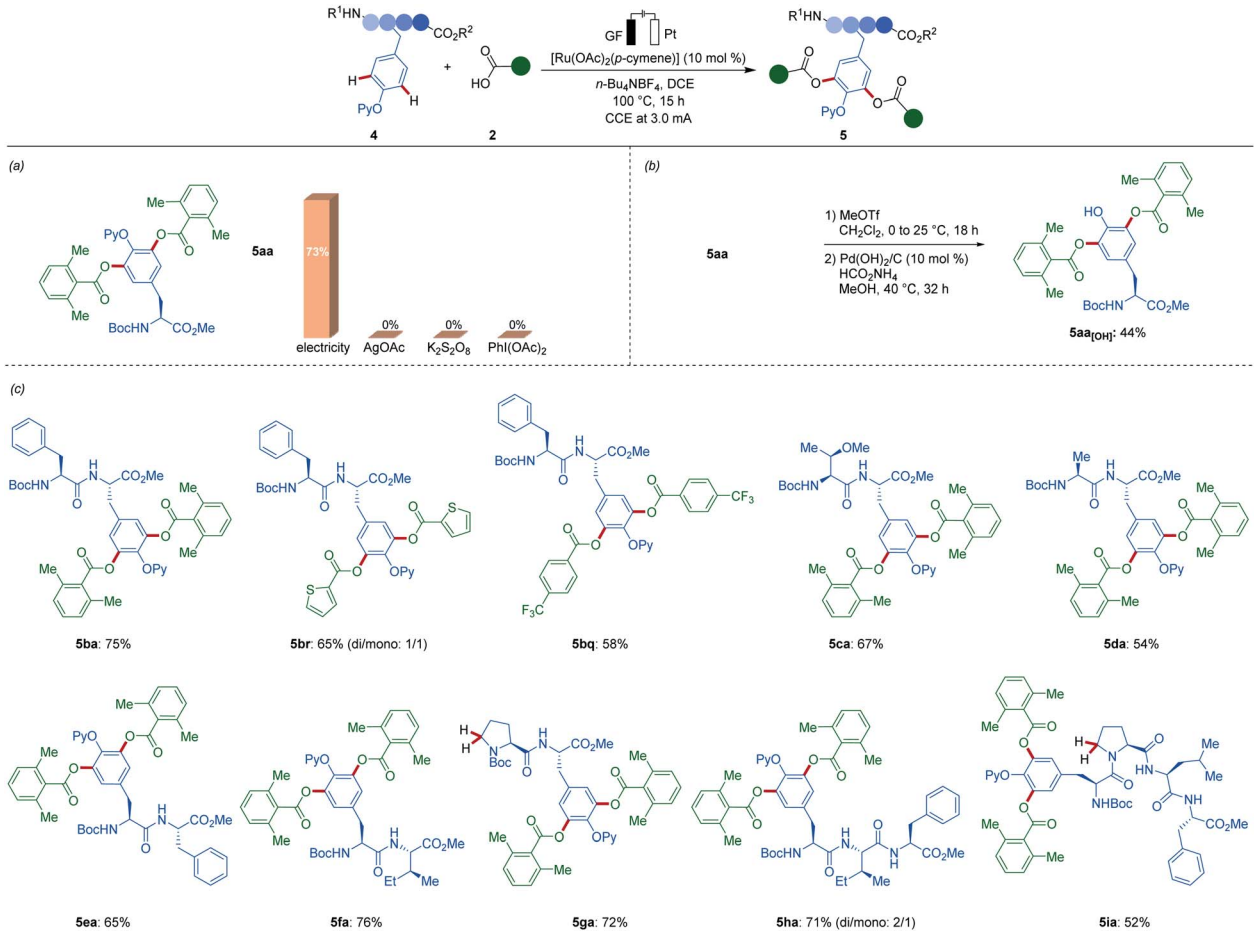
with graphite felt (GF) and platinum plate (Pt) as anode and cathode, respectively (Table 1). After considerable experimentation, the desired product **3aa** was isolated in 87% yield with $[Ru(OAc)_2(p\text{-cymene})]$ (10 mol%), and *n*-Bu_4NBF_4 (1.0 equiv.) in DCE at 100 °C for 15 h (Table 1, entry 1). TFE *in lieu* of DCE at 80 °C afforded a sharp decrease of efficacy (entry 2). With an increase of the temperature, the performance could be improved (entry 3). The direct acyloxylation was not viable in either EtOH or *t*-AmOH/H_2O (3/1) (entries 4 and 5). Other ruthenium catalysts proved less effective for the C–H acyloxylation (entries 6–8). Remarkably, ruthenium catalyst outperformed rhodium(III), iridium(III) and cobalt(III) complexes under otherwise identical reaction conditions (entries 9–12). Control experiments verified the essential role of the ruthenium catalyst and the electricity (entries 13 and 14).

With the optimised reaction conditions in hand, we next explored alternative N-heterocycles, such as pyrimidine **1b** and benzo[*d*]oxazole **1c**, which also set the stage for effective electro-oxygenations (Scheme 1). The substrate scope of the ruthenaelectro-catalyzed C–H acyloxylation was subsequently examined with a representative set of phenols **1** (Scheme 1). Thus, decorated phenols **1** chemo-selectively afforded the desired acyloxylated products **3**. Electron-rich as well as electron-deficient substrates were amenable to the ruthenaelectro-catalyzed acyloxylations. Remarkably, the C–H acyloxylation of naphthalene **1f** occurred site-selectively in the β-position, bypassing a potential *peri*-functionalization regime.

Our attention was then shifted to explore viable carboxylic acids **2** for the ruthenaelectro-catalyzed acyloxylation (Scheme 1). Both electron-rich and electron-deficient acids delivered good to excellent yields, while electron-deficient acids exhibiting slightly better reactivity. Substituted benzoic acids were efficiently converted to the desired products **3ab–3av.** Notably, various sensitive functional groups, including halogens, ester and free hydroxy groups, were fully tolerated under our electrocatalysis. The arene-ligand free $RuCl_3\cdot 3H_2O$ catalyst was also efficient for the ruthenaelectro-catalyzed C–H acyloxylation, suggesting a *p*-cymene-free mode of action (*vide infra*). Heteroaromatic acid, such as the thiophene derivative **2r,** was also a viable substrate. The power of the ruthenium-catalyzed oxygenations was highlighted by the successful use of alkyl carboxylic acids, such as substrates **2s** (acetic acid), **2t** (isobutyric acid), **2u** (cyclopentanoic acid), and **2v** (1-adamantanecarboxylic acid).



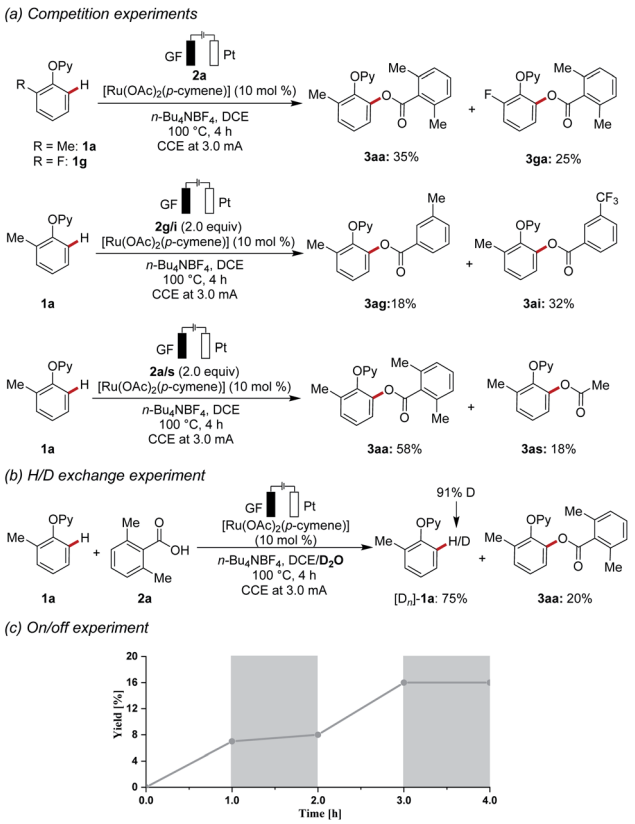
Scheme 1 Substrate scope of acyloxylation with phenols **1** and carboxylic acids **2**. [a] $RuCl_3\cdot 3H_2O$ (10 mol%) as the catalyst.



Scheme 2 Late-stage tyrosine and peptide diversification: (a) evaluation of oxidants, (b) removal of pyridyl group, (c) scope of viable peptides **4**.

The ruthena-electrocatalysis was not limited to the conversion of simple phenols. Next, we devised the envisioned ruthenaelectro-catalyzed late-stage functionalization of tyrosine-containing peptides (Scheme 2). The electrocatalysis avoided the use of stoichiometric oxidants that severely jeopardizes the sustainability and robustness of the late-stage functionalization.[22] To our delight, when amino acid **4a** was utilized, the desired acyloxylated tyrosine derivative **5aa** was selectively obtained. When chemical oxidants were used instead of electricity, the desired oxygenated product was not obtained, providing a strong testament to the robust nature of our electrochemical approach. Moreover, the traceless removal of the pyridyl group was accomplished by a selective methylation/hydrogenation protocol giving rise to NH-free tyrosine-containing acyloxylated amino acid **5aa**$_{[OH]}$. Furthermore, various di-, tri- and tetrapeptides **4b–4i** were efficiently functionalized with various (hetero)aromatic acids **2** without signs of epimerization of the sensitive peptides. Remarkably, our mild electroxidative regime bypassed Shono-type manifolds, even when employing proline-containing di- and tetrapeptides **4g** and **4i**. The broad scope showcased the remarkable efficiency and functional group tolerance of our ruthenaelectro-catalyzed acyloxylations.

Intrigued by the versatility of the electrochemical C–H acyloxylation, we became interested to probe its mode of action. To this end, an intermolecular competition experiment between electronically differentiated phenols **1** was conducted (Scheme 3a). Electron-rich substrate **1a** showed an inherently higher reactivity as compared to electron-deficient substrate **1g**, showing that nucleophilicity rather than kinetic C–H acidity leads to faster reactions. This observation is not in line with a concerted protonation-deprotonation (CMD) mechanism. Instead, a base-assisted internal electrophilic-type substitution (BIES) mechanism is likely operative. Competition experiments, which were designed to investigate the relative reactivities of electronically-differentiated carboxylic acids **2**, showed that the electron-deficient aromatic carboxylic acids **2i** reacted faster (Scheme 3a). Furthermore, a competition experiment between aryl and alkyl carboxylic acids **2a** and **2s** (Scheme 3a) illustrated the superiority of aromatic derivatives. Moreover, a ruthenaelectro-catalysis in the presence of isotopically labelled D_2O led to a significant H/D-exchange (Scheme 3b). The H/D scrambling occurred solely at the *ortho*-position, as judged by the re-isolated substrate [D_n]-**1a**, being indicative of a fast C–H activation. To further elucidate the key role of the electricity, an on/off experiment was conducted (Scheme 3c). The formation of

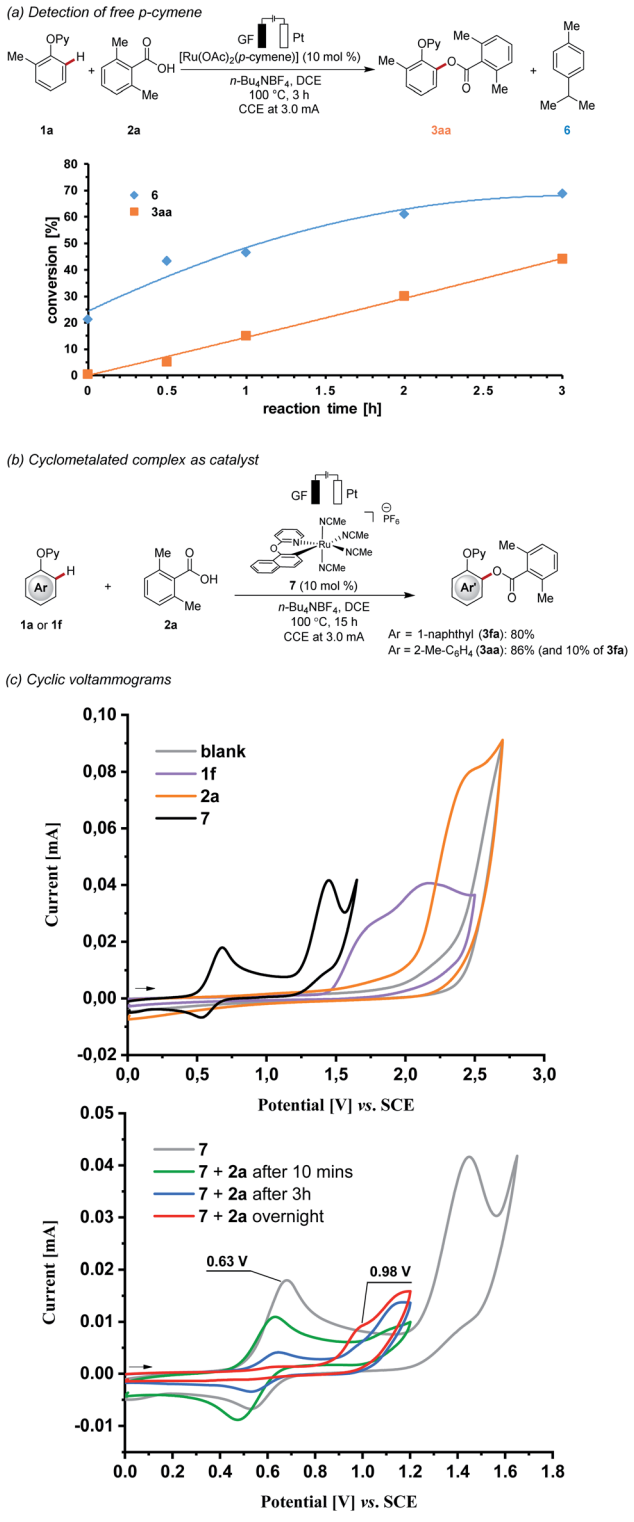


Scheme 3 Key mechanistic findings: (a) competition experiments, (b) H/D scrambling experiment, (c) on/off experiment.

the acyloxylated product was fully suppressed in the absence of the electric current, thereby ruling a radical-chain process out.

During the course of the electrocatalysis, a considerable amount of free *p*-cymene from the [Ru(OAc)$_2$(*p*-cymene)] was observed (Scheme 4a). This finding is indicative of a *p*-cymene-ligand-free complex being catalytically relevant.[23] Next, we prepared the well-defined cationic cyclometalated ruthenium complex 7, which showed high catalytic activity under otherwise identical reaction conditions (Scheme 4b). Kinetic studies revealed comparable reactivities for [Ru(OAc)$_2$(*p*-cymene)] and ruthenacycle 7, as judged by the corresponding initial rates (Fig. S3†).[24] With the proposed key intermediate in hand, we probed its redox properties under electrocatalytic conditions (Scheme 4c). Hence, detailed studies by cyclic voltammetry revealed that the complex 7 underwent reversible oxidation to ruthenium(III) at 0.63 V, being significantly lower than the substrates **1f** and **2a**. Interestingly, the addition of carboxylic acid (*e.g.* 10 equiv.) slowly led to the gradual disappearance of the reversible peak at 0.63 V, and a new irreversible oxidation peak appeared at 0.98 V. Combined with the analysis from the high-resolution mass spectrometry monitoring of the mixture solution after cyclic voltammetry, carboxylate ions were found to replace acetonitrile to coordinate with the metal centre (Fig. S8†).[24] These findings are suggestive of a carboxylate-ligated, arene-ligand-free ruthenacycle as a key intermediate in the C–O reductive elimination.

In order to gain better insights into the catalyst mode of action, density-functional theory (DFT) calculations were carried out for the oxidatively induced reductive elimination(OIRE)[25] at the PW6B95-D4/def2-TZVP+SMD(DCE)//PBE0-D3BJ/def2-SVP level of theory. In these studies, pathways



Scheme 4 Key mechanistic findings: (a) detection of free *p*-cymene, (b) cyclometalated complex as catalyst, (c) cyclic voltammograms.

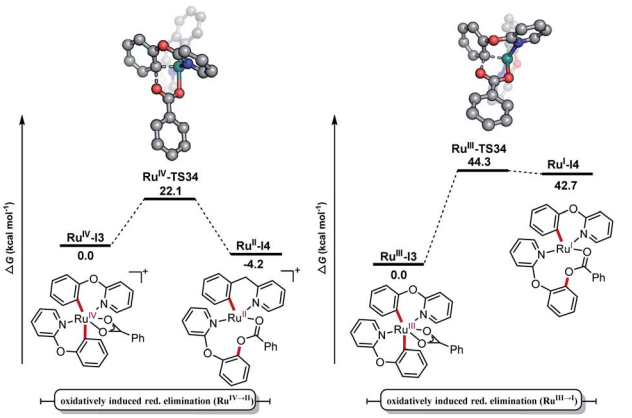
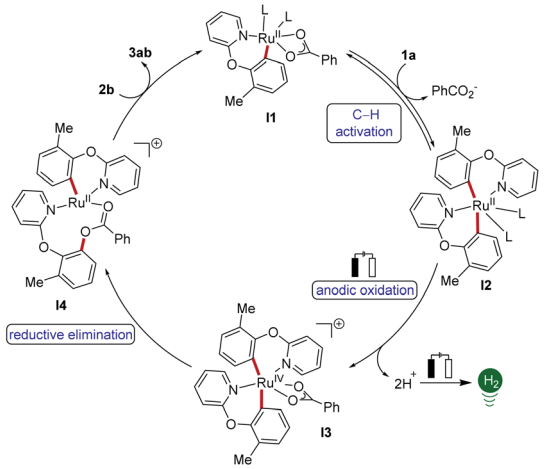


Fig. 2 Computed relative Gibbs free energy profile ($\Delta G_{373.15}$) in kcal mol^{-1} for two distinct *p*-cymene free oxidatively induced reductive elimination pathways at the PW6B95-D4/def2-TZVP+SMD(DCE)//PBE0-D3BJ/def2-SVP level of theory. Non-participating hydrogen atoms were omitted for clarity.



Scheme 5 Proposed catalytic cycle.

starting from ruthenium(III) as well as from ruthenium(IV) were considered (Fig. 2). Three computational models were taken into account: (i) *p*-cymene and 2-phenoxypyridine are coordinated to the ruthenium centre (Fig. S9†),[24] (ii) two 2-phenoxypyridines are coordinated, but one of them serves solely as a L-type ligand (Fig. S10†)[24] and (iii) both substrates are C–H activated but only one is involved in the reductive elimination (Fig. 2). The first two paths could be ruled out, because they revealed energetically disfavoured due to the high calculated barriers. These results are in good agreement with the experiments, where free *p*-cymene was detected during the reaction. With regards to potential bis-cyclometalated intermediate,[26] the ruthenium(II/IV) manifold pathway was shown to be energetically preferred over the ruthenium(I/III) manifold pathway by 22.2 kcal mol^{-1}. Thus, our computational findings provide strong support for a preferential oxidatively induced reductive elimination through bis-cyclometalated ruthenium(IV) species.

On the basis of our findings, a plausible catalytic cycle for the acyloxylation commences with a BIES C–H metalation[27] and dissociation of *p*-cymene, thereby forming the cyclometalated complex **I1** (Scheme 5). A second molecule of **1a** coordinates to ruthenium complex **I1** and undergoes C–H activation to form bis-cyclometalated complex **I2**, which undergoes anodic oxidation to deliver the ruthenium(IV) intermediate **I3**. Finally, reductive elimination and ligand exchange deliver the product **3** and regenerate ruthenacycle **I1**.

Conclusions

In summary, experimental and computational mechanistic studies unraveled a C–H acyloxylation manifold through an arene-ligand-free ruthenium complex. Detailed CV studies and DFT computation provided strong support for the formation of a bis-cyclometalated complex as well as an oxidation-induced reductive elimination process within a ruthenium(II/IV/II) manifold. Our strategy provided an expedient access to a plethora of peptides by modular late-stage acyloxylations of tyrosine-derived peptides.

Data availability

All experimental data, procedures for data analysis and pertinent data sets are provided in the ESI.†

Author contributions

X. H. and L. A. conceived the project. X. H., N. K., J. F. and T. O. performed the experiments. B. Y. performed DFT calculations. A. M. M. assisted X. H. to make the intermediate complexes. X. H. and L. A. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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