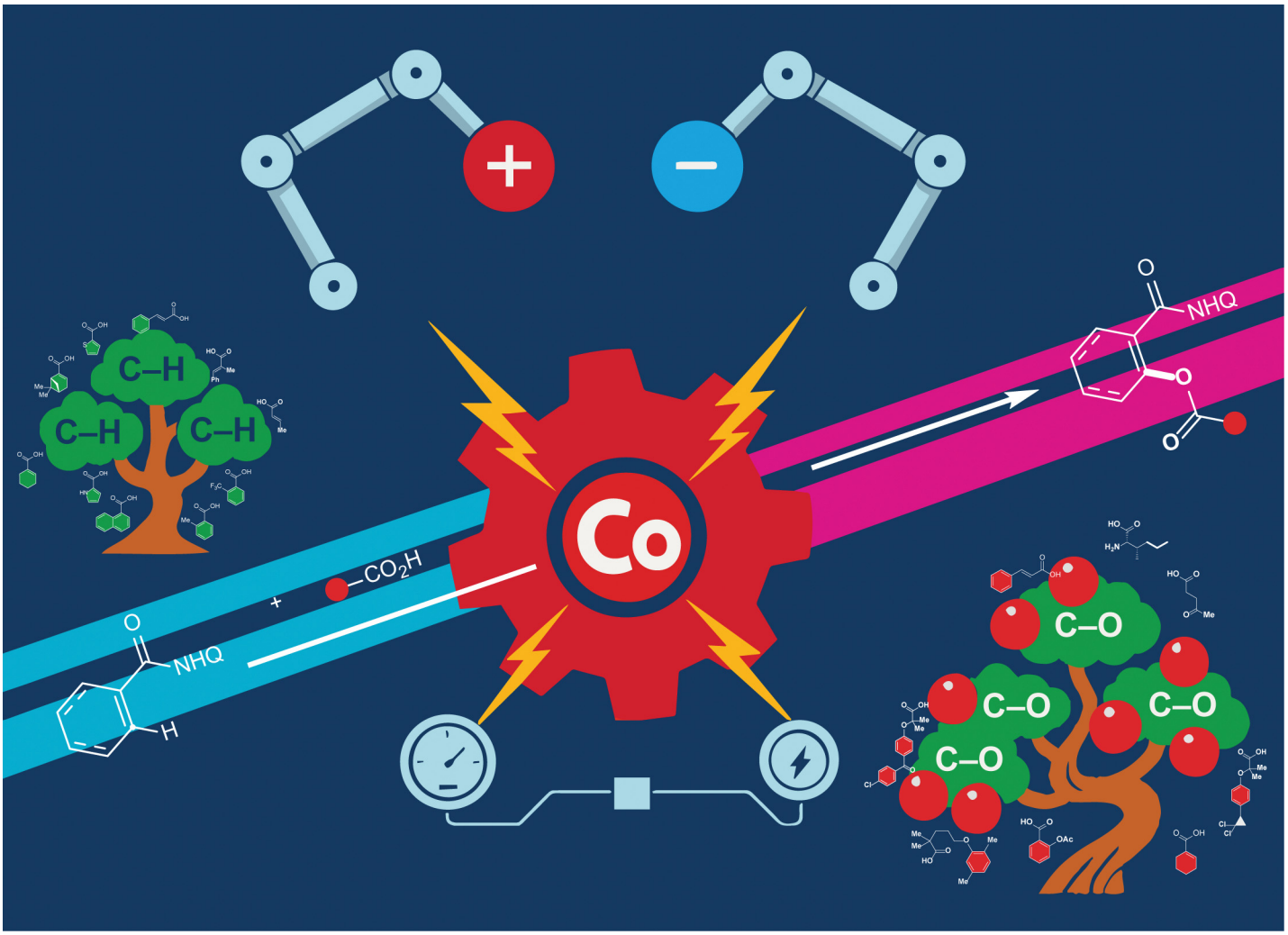

Showcasing research from Professor Oscar Verho's laboratory, Department of Medicinal Chemistry, Uppsala University, Uppsala, Sweden.

Cobaltaelectro-catalyzed C–H acyloxylation of aromatic and vinylic amide derivatives at room temperature

Like a molecular engine, a cobalt electrocatalyst transforms ubiquitous C–H bonds into a rich harvest of valuable esters. This mild and sustainable method enables the direct formation of C–O bonds, yielding a diverse range of complex molecules for biomedical and industrial applications.

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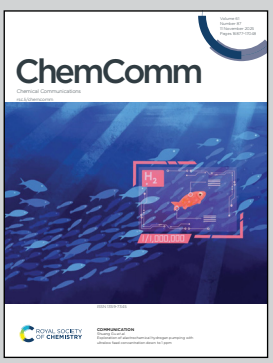

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Cobaltaelectro-catalyzed C–H acyloxylation of aromatic and vinylic amide derivatives at room temperature

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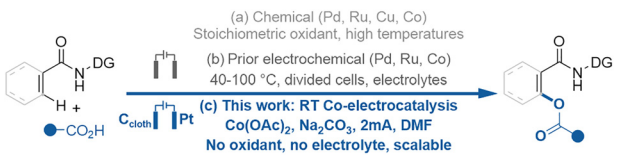
9wHerein, we report a mild and efficient cobalt-catalyzed electrochemical method for the regioselective C–H acyloxylation of aromatic and vinylic amides, utilizing 8-aminoquinoline as the directing group. Notably, this protocol requires no stoichiometric oxidants and operates at room temperature in an undivided cell setup, providing sustainable access to a diverse set of *ortho*-acyloxylated products with broad functional group tolerance.

Direct C–H functionalization has emerged as a transformative strategy in organic synthesis, enabling the streamlined construction of complex molecules from readily available feedstocks.[1,2] Among the diverse repertoire of C–H transformations, C–O bond formation, specifically through acyloxylation, remains a highly desired objective due to the widespread occurrence of ester moieties in pharmaceuticals, materials, and natural products.[3] While traditional esterification methods generally require substrate pre-functionalization along with the generation of stoichiometric byproducts,[4–16] direct C–H acyloxylation offers a powerful and atom-economical alternative. Although cobalt catalysis has shown considerable success in many realms of C–H activation, achieving efficient and selective C–O bond formation has proven challenging previously.[4–8,17] Early work by Kochi *et al.* demonstrated the feasibility of cobalt-mediated C–O bond construction,[18,19] yet efficient catalytic systems remained elusive.

Nevertheless, cobalt-catalyzed C–H oxygenation has significantly progressed in recent years. Zeng and co-workers described a cobalt-catalyzed cross-dehydrogenative coupling (CDC) of arenes with carboxylic acids (Scheme 1(a)), establishing a valuable precedent for accessing aryl esters through proposed aryl-Co(III) species.[20] Ackermann and co-workers further advanced the field with an elegant electrochemical cobalt-catalyzed C–H oxygenation protocol (Scheme 1(b)), demonstrating mild and selective oxygenation of both arenes and alkenes under electrocatalytic conditions, which circumvented the need for stoichiometric chemical oxidants.[21–23] Complementary to these cobalt-catalyzed approaches, copper-catalyzed or copper-mediated acyloxylations (Scheme 1(b)) have also been developed.[9–12] The copper-based methods underscore the effectiveness of bidentate ligands in promoting site-selective C–H functionalization. Further expanding the C–O bond formation landscape, Jeganmohan and Padala reported a ruthenium-catalyzed protocol for the *ortho*-benzoxylations of benzamides.[24]

Building on the success of 8-aminoquinoline (8-AQ) as a bidentate directing group in C–H arylation,[25–27] we envisioned an electrochemical C–H acyloxylation strategy for aromatic and vinylic amides. The 8-AQ directing group has previously demonstrated a remarkable ability to facilitate selective C–H activation, offering promising prospects for regioselective acyloxylation. Furthermore, recent reports on electrochemical C–H acyloxylation,[28–36] provide compelling evidence for the feasibility and potential of this approach. Several studies have successfully demonstrated electrochemical acyloxylation, highlighting the method's mild and practical nature. These precedents highlight the potential of electrochemistry to avoid harsh conditions and stoichiometric oxidants. A variety of substrates, including aromatic amides,[28,33–35] phenols,[36] 2-phenylpyridines,[29] and 8-methylquinoline[33] have been successfully acyloxylated using electrochemical methods, showcasing the versatility of this approach.



Scheme 1 Strategies for C–H Acyloxylation. (a) Chemical methods, requiring harsh conditions. (b) Prior electrochemical methods. (c) This work: cobalt–electrocatalyzed C–H acyloxylation in an undivided cell at room temperature.

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Herein, we report a novel electrochemical cobalt-catalyzed method for the direct C–H acyloxylation of aromatic and vinylic amides, utilizing the 8-AQ directing group. Recognizing the limitations of existing C–H acyloxylation methods, particularly the reliance on precious metals and harsh reaction conditions, we pursued a protocol prioritizing sustainability and practicality. Inspired by the seminal contributions of Zeng[20] and others,[9–12,21,24] we sought to harness the combined power of cobalt as an earth-abundant, first-row transition metal catalyst and electrochemistry to develop a cost-efficient C–H acyloxylation methodology.[37,38] Inspired by Ackermann's work,[21,28] we employed mild, reagent-free electrochemical conditions to eliminate stoichiometric oxidants and enable precise reaction control. Finally, *in situ* generated sodium carboxylates provide ionic conductivity to the reaction mixture. These external supporting electrolyte-free conditions simplify reaction analysis, improve sustainability, and streamline the synthetic route to valuable acyloxylated amide compounds, exhibiting broad substrate scope and functional group compatibility.[38,39]

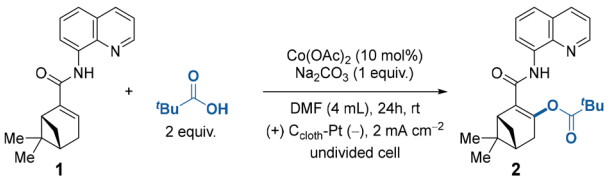
Our initial efforts focused on the electrochemical acyloxylation of (1*R*,5*S*)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-(myrtenoyl) *N*-(quinolin-8-yl)-carboxamide **1** with pivalic acid. Selected entries from this optimization study are shown in Table 1. Employing a carbon rod anode and a platinum plate cathode for a DMF solution of $Co(OAc)_2{\cdot}4H_2O$ as a catalyst and KOPiv as the base afforded product **2** in 53% yield and provided an encouraging starting point for further optimizations (entry 2). A brief catalyst screening identified $Co(OAc)_2{\cdot}4H_2O$ as a superior alternative to $Cu(OAc)_2$ or $Ni(OAc)_2$, which showed no activity under comparable reaction conditions (entry 3). Changing the base to Na_2CO_3 in this reaction system was beneficial and led to a slight improvement in the yield (57%, entry 4). However, a more pronounced improvement in reaction performance was observed when the anode material was changed to carbon cloth and the current was lowered to 2 mA, resulting in 95% yield of the desired product **2** (entry 1).

A solvent screen performed under these improved reaction conditions established DMF as the optimal solvent for this transformation (entry 5). Lowering the current density to 1 mA cm^{-2} resulted in a slightly diminished yield (91%) of product **2** (entry 6). Moreover, switching to other inorganic carbonate bases such as Li_2CO_3, K_2CO_3, and Cs_2CO_3 resulted in a lower yield of product **2**, when compared to Na_2CO_3 (entries 7–9). No product formation occurred without an applied potential, confirming the essential role of electrochemistry (entry 10). It is also worth noting that anhydrous $Co(OAc)_2$ exhibited comparable activity to the tetrahydrate (entry 11).

With the optimized conditions in hand, we next explored the scope of the electrochemical C–H acyloxylation of both vinylic and aromatic amides (Scheme 2). We first investigated the scope using the 8-AQ amide of myrtenic acid **1** with various carboxylic acids. The reaction tolerated sterically demanding aliphatic acids like pivalic acid (**2**, 84%) and cyclohexanecarboxylic acid (**3**, 65%). Aromatic carboxylic acids, including those with electron-donating and electron-neutral substituents, also reacted efficiently to provide esters **5** (66%) and **6** (72%). The scope was then extended by the coupling of a range of vinylic amides with 1-methyl-1*H*-pyrrole-2-carboxylic acid, smoothly delivering products **7–10** in 35–91% yield.

The methodology was equally effective for aromatic C–H acyloxylation. For example, the 1-naphthoic acid-derived amide proved to be an excellent substrate, reacting with a diverse array of acids forming products **11–14** in 68–83% yield. Notably, the protocol was compatible with additional functional groups, such as the ketone in levulinic acid (**12**, 83%) and the Boc-protected amino acid moiety of isoleucine (**14**, 70%), showcasing its potential for peptide modification. Substituents on the benzamide ring were well-tolerated; both methyl-substituted

Table 1 Optimization of the electrochemical C–H acyloxylation[a]



Entry	Variation from standard conditions[a]	Yield[b]
1	**None**	**95%**
2	C_{rod}/Pt; 4 mA; KOPiv (3 equiv.) instead of Na_2CO_3	53%
3	$Cu(OAc)_2$ or $Ni(OAc)_2$ instead of $Co(OAc)_2{\cdot}4H_2O$	0%
4	C_{rod}/Pt	57
5	AcOH, DCE, DMSO, MeCN, MeOH, or *t*-AmOH instead of DMF	0–28%
6	1 mA cm^{-2}	91%
7	Li_2CO_3 (1 equiv.) instead of Na_2CO_3	33%
8	K_2CO_3 (1 equiv.) instead of Na_2CO_3	49%
9	Cs_2CO_3 (1 equiv.) instead of Na_2CO_3	0%
10	No electricity	0%
11	Anhydrous $Co(OAc)_2$ instead of $Co(OAc)_2{\cdot}4H_2O$	90%

[a] Reaction conditions: substrate **1** (0.2 mmol), pivalic acid (2 equiv.), catalyst (10 mol%), base, solvent (4 mL), electrode, constant current, rt, carbon cloth anode (1 cm^2), and a platinum plate cathode (1 cm^2), unless otherwise noted. [b] Yields determined by NMR with 1,3,5-trimethoxybenzene as an internal standard.

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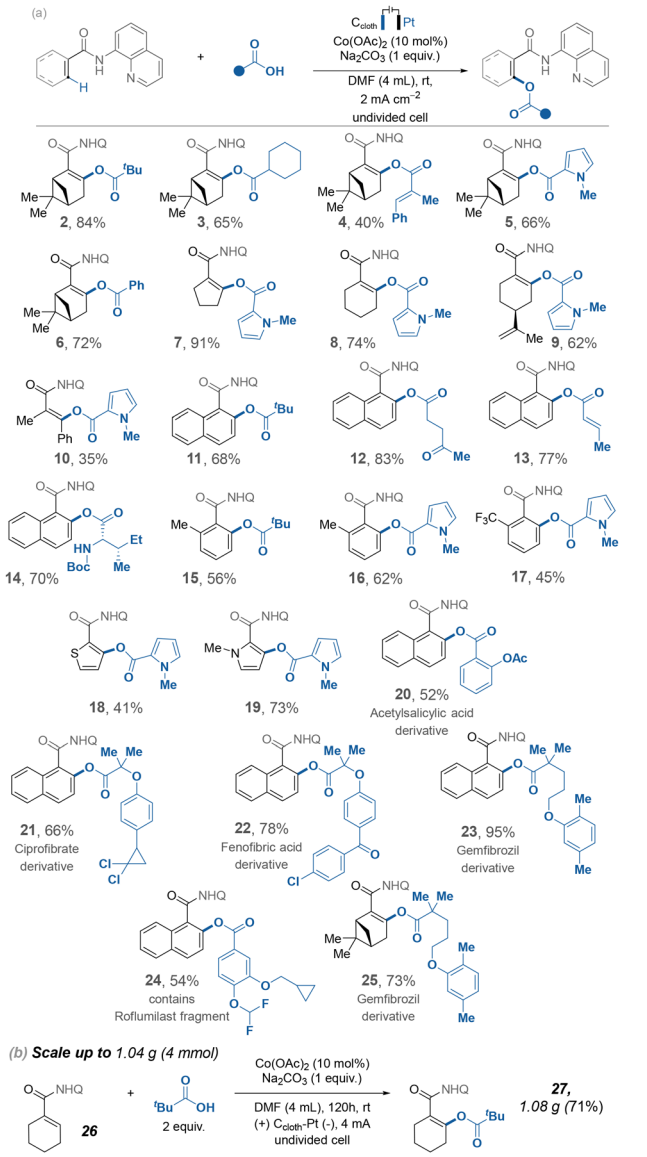


Scheme 2 Substrate scope investigation: (a) reagents and conditions: amide (1.0 equiv.), acid (2.0 equiv.), $Co(OAc)_2$ (10 mol%), Na_2CO_3 (1 equiv.), DMF (4 mL), 2 mA, 24 h, rt, carbon cloth anode (1 cm^2) and platinum plate cathode (1 cm^2). Yields refer to isolated yields following column chromatography. Q = 8-quinolinyl directing group. (b) Scale-up of the present electrochemical C–H acyloxylation protocol.

(**15** and **16**) and CF_3-substituted (**17**) amides delivered the desired products, although the electron-deficient substrate required a slightly higher catalyst loading. The protocol could also be extended to heteroaromatic amides, providing acyloxylated thiophene and pyrrole derivatives (**18** and **19**).

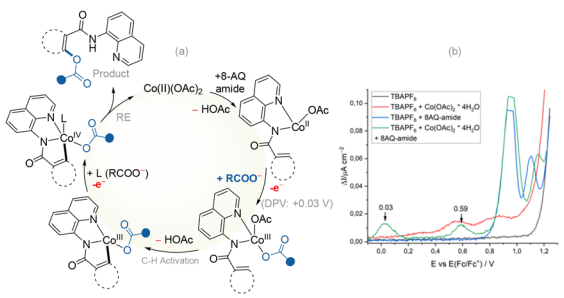
To underscore the practical utility of this method for late-stage functionalization, we applied it to complex amides derived from known pharmaceutical agents. We were pleased to find that derivatives of acetylsalicylic acid (**20**), the lipid-lowering drugs ciprofibrate (**21**), fenofibric acid (**22**), gemfibrozil (**23** and **25**), and the COPD medication roflumilast (**24**) were all acyloxylated in good to excellent yields (54–95%). These results demonstrate the method's potential for rapidly generating novel analogues of biologically active molecules with minimal synthetic effort.

Gratifyingly, the protocol for C–H acyloxylation can easily be scaled up to the gram-scale, as exemplified by the reaction of cyclohexene–carboxamide **26** (Scheme 2, bottom). The reaction was performed on a 4.0 mmol (1.08 g) scale and the desired product **27** could be isolated in 71% yield.

The mechanism of the analogous metallaelectro-catalyzed transformations has been studied and reported previously.[23,25] As depicted in Scheme 3, a catalytic cycle is proposed to comprise an irreversible, turnover-determining C–H activation to form a Co(III)-cyclometalate (**C**), which is subsequently oxidized to a Co(IV) species (**D**).[40,41] The latter is followed by carboxylate coordination and upon C–O bond-forming reductive elimination, the product (**E**) is released, and the catalyst is regenerated to the resting state.

Mechanistic studies support the proposed pathway (Scheme 3). An "ON/OFF" experiment confirmed the reaction is current-dependent, ruling out a radical chain mechanism (S15). Irreversible C–H activation was confirmed by H/D scrambling experiments (S16), while UV-Vis and ^{1}H NMR monitoring supported the formation of a diamagnetic Co(III) species upon electrolysis (S17 and S18).

In addition, electroanalytical techniques were employed to understand the catalyst–substrate redox relationship. The state-of-the-art cyclic voltammetry (CV) were found largely uninformative in our case. Instead, differential pulse voltammetry (DPV) was employed as a method of choice, offering more sensitive detection of redox events (Scheme 3 and Fig. S3–S10). The anodic stability of carboxylates with electron donating groups is known to be poor $E_{Red} > 0.2$–0.5 V *vs.* E_{Fc}, therefore model tetrabutylammonium hexafluorophosphate ($TBAPF_6$) was taken to investigate electrochemical behaviour of reactants. Still, oxidation of DMF itself was observed to set on at $E_{Red} > +1.2$ V *vs.* E_{Fc}. Under such conditions, oxidation of $Co(OAc)_2$ can be seen as two weak peaks at *ca.* +0.55 and +0.85 V_{Fc}, assumed to be Co(III) and Co(IV). The poor detectability can be rationalized by the absence of specific adsorption and pronounced electrostatic migration of cationic cobalt salts in DMF away from the anode. Substrate **35** under DPV conditions is featured by two strong peaks at +0.95 and +1.10 V_{Fc}, representing formation of radical–cation and cation species of the quinoline



Scheme 3 Plausible mechanism of cobaltaelectro-catalyzed C–H acyloxylation. (a) Proposed catalytic cycle. (b) Differential pulse voltammetry of reaction mixture components under model conditions.

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scaffold. Interestingly, the mixing of both **35** and $Co(OAc)_2$ gave a rise of two new peaks, indicating a complexation process that is highly reversible, as peaks of non-coordinated ligands are still observable. This observation rationalizes the need for a low current density under preparative conditions using high–surface area carbon cloth, in order to maintain a sufficiently low potential and avoid oxidation of the carboxylate or DMF.

In conclusion, we have developed an efficient cobaltaelectrocatalyzed C–H acyloxylation method for aromatic and vinylic amides using 8-AQ as the directing group. This method allows for the synthesis of a wide range of acyloxylated amide compounds in good to excellent yields in an operationally simple, undivided cell setup. The electrochemical approach reduces the reliance on stoichiometric chemical oxidants, making the protocol more sustainable. This work highlights the potential of combining cobalt catalysis and electrochemistry for efficient and green C–H functionalization.

R. S.: investigation, writing – original draft. P. N.: investigation, writing – review & editing. L. M.: investigation. O. V.: conceptualization, supervision, funding acquisition, writing – review & editing. All authors have given approval to the final version.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting the findings of this study are available within the article and its supplementary information (SI). Supplementary information is available. See DOI: **https://doi.org/10.1039/d5cc04394h**.

Electroanalytical data for this article, are available at Zenodo at **https://doi.org/10.5281/zenodo.16640616**.

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