

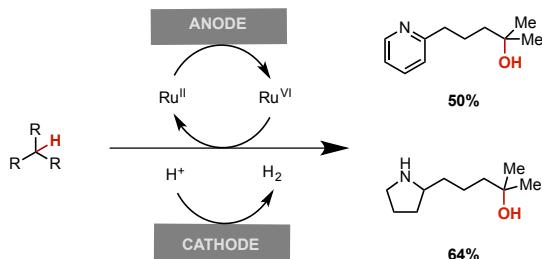
Electrochemical Ruthenium-Catalyzed C–H Hydroxylation of Amine Derivatives in Aqueous Acid

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Supporting Information Placeholder



ABSTRACT: The development of an electrochemically-driven, ruthenium-catalyzed C–H hydroxylation reaction of amine-derived substrates bearing tertiary C–H bonds is described. The reaction is performed under constant current electrolysis in a divided cell to afford alcohol products in yields comparable to those of our previously reported process, which requires the use of stoichiometric H_5IO_6 for catalytic turnover. With aqueous acid as solvent, the cathodic electrode reaction simply involves the reduction of protons to evolve hydrogen gas. The optimized protocol offers a convenient, efficient, and atom-economical method for sp^3 -C–H bond oxidation.

Catalytic methods for selective C–H bond oxidation are enabling technologies for total synthesis and medicinal chemistry.¹ The applicability of such processes has advanced with the design of catalysts that oxidize specific C–H bonds in the presence of common functional groups.^{2,3} To this end, we recently reported a C–H hydroxylation method employing a *cis*-bis(4,4'-di-*tert*-butyl-bipyridine)ruthenium complex (*cis*-Ru(dtbpy)₂Cl₂, **1**) that operates in acidic aqueous media to achieve selective oxidation of 3° and benzylic C–H bonds in the presence of basic amines and heteroaromatic structural motifs.⁴ The acidic solvent conditions suppress amine and heterocyclic amine *N*-oxidation.⁵ This process is compatible with structurally disparate substrates, including select active pharmaceutical ingredients and natural product derivatives. Nonetheless, a limitation of the current method is the requirement for the use of super-stoichiometric amounts of a chemical oxidant (periodic acid, H_5IO_6) to effect reasonable catalyst turnover numbers and product yields. The requirement for excess terminal oxidant is a general problem in C–H oxidation catalysis.⁶

Replacement of a bulk chemical oxidant with electrochemical oxidation is well-established and offers an appealing alternative for powering C–H functionalization reactions (Figure 1).⁷ Successful transition from chemical to electrochemical metal-mediated oxidation is contingent on the efficient heterogeneous oxidation of the catalyst.⁸ Cyclic voltammograms (CV) of

catalyst **1** reveal that five oxidation states ($\text{Ru}^{\text{II}}\text{--Ru}^{\text{VI}}$) are electrochemically accessible over a span of 800 mV in aqueous acid (Figure 2). As previously reported by Meyer and co-workers, the $\text{Ru}^{\text{III/IV}}$ couple is kinetically slow to form at the electrode and thus not observed on the timescale of the CV recording.⁹

Mechanistic studies of reactions with **1** demonstrated that catalytic currents occur for both the $\text{Ru}^{\text{IV/VI}}$ and $\text{Ru}^{\text{V/VI}}$ couples.¹⁰ This finding suggested that the active catalyst species, believed to be an oxo- or dioxo-Ru(V) or Ru(VI) intermediate, can be readily accessed through outer-sphere oxidation, thus motivating the development of an electrochemical protocol for C–H hydroxylation. The operation of **1** in aqueous acid was also considered advantageous for the development of an electrochemical method, as the ionic medium would serve as supporting electrolyte. Accordingly, no screening of supporting electrolyte was necessary. Furthermore, the strongly acidic ($\text{pH} < 1$) aqueous conditions enabled simple proton reduction ($2\text{H}^+ + 2\text{e}^- \rightarrow \text{H}_2$) to function as the cathodic reaction (Figure 1), a notable difference between

Previously reported C–H hydroxylation with chemical oxidant



This work: electrochemical C–H hydroxylation protocol

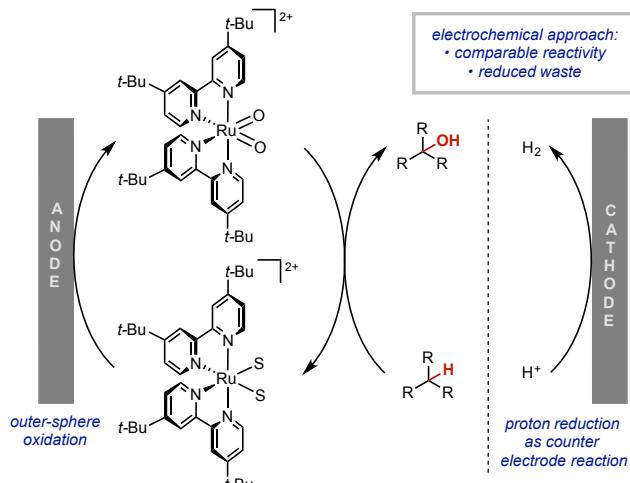


Figure 1. Comparison between chemical and electrochemical approaches for C–H hydroxylation.

electrocatalysis in aqueous versus non-aqueous solvents. The latter requires addition of a supporting electrolyte salt and the precise reaction occurring at the counter electrode is often unclear.

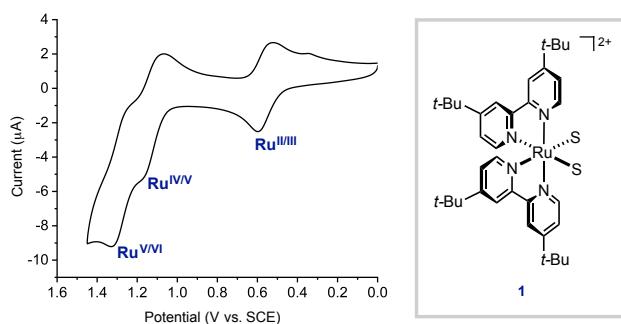


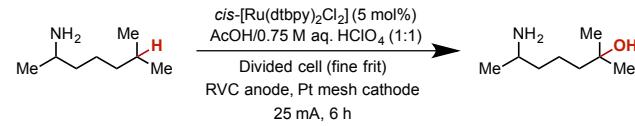
Figure 2. Cyclic voltammogram (CV) of 1 mM *cis*-[(dtbbpy)₂Ru(CO₃)]¹¹ in 1:1 AcOH/0.75 M aqueous HClO₄ at a 10 mV/s scan rate using a glassy carbon working electrode, platinum mesh counter electrode, and SCE reference electrode.

Initial proof-of-concept studies focused on establishing the feasibility of the electrochemical hydroxylation by **1** with a commercially available model substrate, 2-amino-6-methylheptane (Table 1). This primary amine substrate was selected for its high solubility in aqueous acid. In CV studies of **1**, the different redox couples are more clearly distinguished in aqueous perchloric acid than in aqueous triflic acid, thus the reaction was optimized using the former.^{10,12} Several parameters were altered in an effort to find optimal electrochemical reaction conditions, including the choice of electrode materials, cell configuration, and electrochemical settings (i.e., controlled potential vs. constant current electrolysis).

Electrochemical oxidation of 2-amino-6-methylheptane by **1** does not proceed in an undivided cell. The inability to effect hydroxylation of this substrate presumably arises from unproductive reduction at the cathode of the Ru species, all of which are more readily reduced than protons based on their differing redox potentials.¹³ Thus, a H-cell with the anodic and cathodic chambers separated by a fine glass frit was employed for all subsequent screening. In this divided cell, the reaction contents are loaded into the anodic chamber with 4 mL of 1:1 AcOH/0.75 M aqueous HClO₄; an equivalent volume of 1:1 AcOH/0.75 M aqueous HClO₄ is added to the cathodic chamber.

Electrochemical oxidation was initially attempted by controlled potential bulk electrolysis to generate a discrete Ru^V-based oxidant. Our previous mechanistic studies showed that one pathway for catalyst arrest involved ligand dissociation, a reaction postulated to ensue from a Ru^{VI} dioxo species.^{9,10} Notably, oxo species of both Ru^{VI} and Ru^V were established as active catalysts, but ligand dissociation is only believed to occur from the former.⁹ Accordingly, we envisioned employing controlled potential electrolysis to selectively generate a Ru^V oxidant in order to suppress the putative catalyst decomposition pathway. In practice, however, controlled potential electrolysis required excessively long reaction times as a consequence of sluggish electron transfer kinetics at the anode (Table 1, entry 3–4). This result is not particularly surprising given that relatively slow CV scan rates (<50 mV/s) are necessary to observe clear redox events with **1**.

Table 1. Analysis of Electrolysis Conditions for C–H Hydroxylation^a



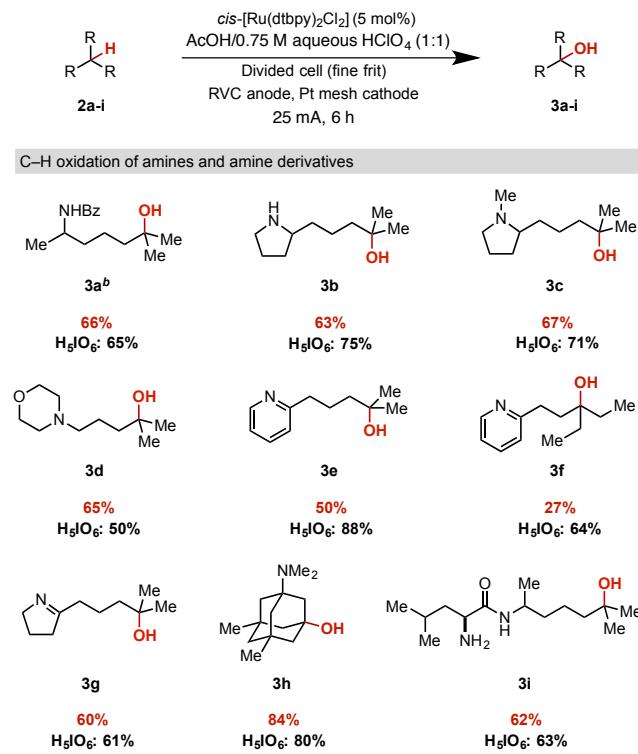
entry	deviation from standard conditions	yield ^b (%)
1	none	63
2	chemical oxidant conditions ^c	65
3	1.34 V vs. SCE (Ru ^V), 24 h	15
4	1.27 V vs. SCE (Ru ^V), 24 h	<5
5	4 h	36
6	10 mA	35
7	10 mA, 14 h	51
8	20 mA, 14 h	63
9	35 mA	51
10	50 mA	30
11	no <i>cis</i> -Ru(dtbbpy) ₂ Cl ₂	0
12	2.5 mol% <i>cis</i> -Ru(dtbbpy) ₂ Cl ₂	48
13	no current	0
14	undivided cell	<5

^aReactions conducted on a 0.24 mmol scale. ^bPercent yield determined by ¹H NMR integration of unpurified reaction mixtures versus 4-nitrotoluene as internal standard. ^cChemical oxidant conditions: 5 mol% *cis*-Ru(dtbbpy)₂Cl₂, 2 equiv H₅IO₆, 1:1 AcOH/H₂O, 6 equiv TfOH, 4 h. SCE = saturated calomel electrode.

A marked improvement in reaction performance was noted by switching from constant potential to constant current (CC) bulk electrolysis. Performing the CC electrolysis reaction with 2-amino-6-methylheptane at 10 mA for 6 h afforded a >2-fold

increase in product yield (Table 1, entry 6). Further optimization of this process focused on examining a range of fixed current values for electrolysis. Ultimately, it was determined that performing the reaction at 25 mA for 6 h afforded product in a yield comparable to the optimized chemical oxidation with H_5IO_6 (Table 1, entry 1 vs. 2). Controlling the current, rather than performing electrolysis at constant potential, forces the reaction to proceed by applying a larger overpotential.^{14,15} Monitoring the potential through inclusion of a SCE reference electrode in the anode compartment reveals that the applied potential is 2.5 V when the reaction is performed at 25 mA. This potential is substantially higher than the redox potentials measured by CV for generating the high valent Ru states—the applied potential is over 1 V higher than the onset potential for generation of Ru^{VI} . The need for such a large overpotential reflects the slow electron transfer kinetics for outer-sphere oxidation of the Ru catalyst.¹⁶

Table 2. Substrate Scope of Optimized Electrochemical C–H Oxidation Protocol Compared with Chemical Oxidant Protocol^a



^aReported yields for electrochemical protocol are in red and are of isolated material on a 0.24 mmol scale. All reactions were performed in duplicate. Yields in black are for the chemical oxidant protocol; conditions: 5 mol% *cis*-Ru(dtbpyp)₂Cl₂, 2 equiv H_5IO_6 , 1:1 AcOH/H₂O, 6 equiv TfOH, 4 h. ^bReaction performed with unprotected primary amine, benzoyl protection performed after work-up to facilitate product isolation.

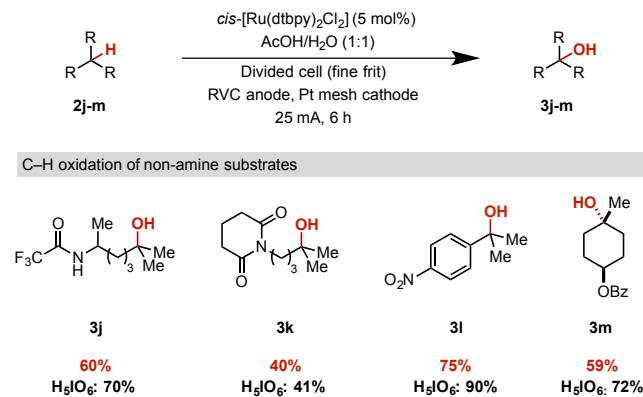
Having identified optimal conditions for controlled current electrolysis, we next examined the scope of this electrochemical C–H hydroxylation protocol. A variety of structurally disparate substrates tested in our earlier report were assessed under the electrochemical protocol for direct comparison of the efficiency of inner- versus outer-sphere oxidation.⁴ Overall, the electrochemical oxidation procedure provides the desired hydroxylated products of basic amine substrates in comparable

yields to the protocol using H_5IO_6 (Table 2). A range of substrates containing oxidatively sensitive nitrogen functional groups are amenable to the reaction conditions, yielding the desired C–H hydroxylation products in moderate-to-high yields. Primary, secondary, and tertiary amines are viable substrates (**3a–d**). A cyclic imine, a memantine derivative, and an unprotected amino acid derivative are also compatible with the reaction conditions, forming the corresponding alcohol products in yields $\geq 60\%$ (**3g–i**).

A notable discrepancy between the chemical and electrochemical protocols is the functional group compatibility of pyridine-derived substrates. Using the latter protocol, reactions of pyridine-derived substrates afford lower product yields (e.g., **3e, 3f**). Furthermore, only 25% of starting material **2e** is recovered from this reaction. The incompatibility of the pyridyl moiety to our conditions for CC electrolysis may be a consequence of direct oxidation of this group at the anode, adsorption of **2e** to the anode, and/or poor aqueous solubility of the substrate.^{16,17}

Substrates lacking basic amine functional groups were also examined under the electrochemical C–H oxidation protocol (Table 3). Strong acid is not necessary in the absence of basic amine-bearing substrates; thus, these reactions can be performed in a 1:1 AcOH/H₂O mixture. Despite the poor solubility of these substrates in the reaction medium, the electrochemical protocol produces the desired 3° alcohol products in comparable yields to the periodic acid protocol. Amides, imides, benzoyl-protected alcohols, and electron deficient arenes are all amenable to electrochemical oxidation. Although not explicitly examined, the slightly lower yields for arene-based substrates may be related to issues similar to those observed with pyridine derivatives.

Table 3. Electrochemical C–H Oxidation Protocol Non-amine Scope Compared with Chemical Oxidant Protocol^a



^aReported yields for electrochemical protocol are in red and are of isolated material on a 0.24 mmol scale. All reactions were performed in duplicate. Yields in black are for chemical oxidant protocol; conditions: 5 mol% *cis*-Ru(dtbpyp)₂Cl₂, 2 equiv H_5IO_6 , 1:1 AcOH/H₂O, 6 equiv TfOH, 4 h.

In summary, this report describes the development of a method for electrochemical, Ru-catalyzed C–H hydroxylation of functionalized, 3° C–H bond-derived substrates. Using electric current to drive catalyst turnover eliminates the need for a super-stoichiometric chemical oxidant without detriment to catalyst performance. The stability of the *cis*-[Ru(dtbpyp)₂Cl₂]

catalyst in aqueous acid and the use of a divided cell enables proton reduction as the cathodic electrode reaction. Future work is ongoing with second-generation Ru-catalysts to further advance this C–H functionalization technology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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- (11) Cyclic voltammograms of Ru-carbonato complexes yield the expected redox events, while dichloro adducts yield featureless

CVs. However, each complex performs comparably in the C–H oxidation reaction.

(12) Reactions performed with chemical oxidant in either aqueous perchloric acid or aqueous triflic acid were found to yield equivalent results.

(13) Proton reduction occurs at -0.242 V vs. SCE, more negative than the Ru^{III/II} reduction peak by > 0.7 V and the Ru^{VI/V} couple by >1.5 V.

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(17) A control reaction conducted with substrate **2e** and no applied current resulted in recovery of 75% of starting material, suggesting that some pyridine substrate is adsorbed onto the RVC anode. However, direct oxidation of the pyridine nucleus and aqueous solubility of the substrate are also likely factors affecting results with these two substrates.