Electrosynthesis Hot Paper

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Rhodium-Catalyzed Electrooxidative C–H Olefination of Benzamides

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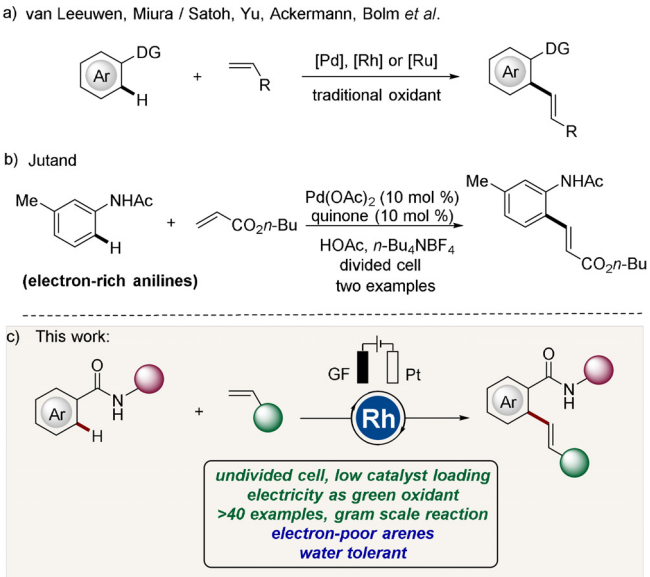
Abstract: *Metal-catalyzed chelation-assisted C–H olefinations have emerged as powerful tools for the construction of functionalized alkenes. Herein, we describe the rhoda-electrocatalyzed C–H activation/alkenylation of arenes. The olefinations of challenging electron-poor benzamides were thus accomplished in a fully dehydrogenative fashion under electrochemical conditions, avoiding stoichiometric chemical oxidants, and with H_2 as the only byproduct. This versatile alkenylation reaction also features broad substrate scope and used electricity as a green oxidant.*

C–H alkenylations have proven to be a powerful tool for C–C bond formation.[1,2] While considerable advances have been accomplished for palladium-,[3] rhodium-,[4] and ruthenium-catalyzed[5] C–H alkenylation reactions by chelation assistance[6] (Scheme 1 a), major challenges continue to be associated with these C–C bond-forming reactions. Among these, pioneering studies were reported by the groups of van Leeuwen,[7] Yu,[8] Miura/Satoh,[9] Glorius,[10] and Ackermann.[11] However, the requirement for toxic and waste-generating stoichiometric oxidants translates into a strong demand for environmentally friendly and atom-economic strategies.

In recent years, electrosynthesis has gained significant attention owing to the use of waste-free and inexpensive electric current as a redox equivalent, thereby avoiding stoichiometric amounts of toxic and costly chemical redox agents.[12–14] However, to the best of our knowledge, there has been only a single report on metal-catalyzed directed C–H olefination using electricity as the oxidant.[15] In 2007, Jutand reported two examples of an electrochemical palladium(II)-catalyzed Fujiwara–Moritani-type reaction, in which benzoquinone was required as a redox mediator in a divided cell setup (Scheme 1 b). Considering that there has been no breakthrough progress in the development of convenient electrooxidative C–H olefination for more than a decade, the development of a general and efficient electrochemical method for alkenylation reactions is in high demand. To this end, we have now unraveled an unprecedented rhodium-catalyzed electrooxidative olefination through the use of benzamides as the substrates, on which we report herein (Scheme 1 c). Salient features of our strategy comprise (a) alkenylations through versatile rhodium catalysis, (b) a user-friendly undivided cell setup, (c) no additional electrolyte, (d) high regio- and monoselectivities, and (e) efficient transformation of inherently electron-deficient benzamides.



Scheme 1. Metal-catalyzed direct C–H activation/alkenylation.

We initiated our studies by probing various reaction conditions for the envisioned electrochemical rhodium-catalyzed C–H alkenylation reaction of benzamide **1a** in a user-friendly undivided cell setup (Table 1). After extensive optimization, we found that the reaction of benzamide **1a** with styrene (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %) and NaOPiv in *t*-AmOH/H_2O (3:1) delivered product **3aa** with 73 % isolated yield (entry 1). Furthermore, we found that NaOPiv was the best base for the reaction, although other carboxylate additives were also effective (entries 2 and 3). Notably, *ortho*-alkenylation of benzamide **1** followed by intramolecular cyclization to provide cyclic lactams was not observed.[16] Attempts to replace the reaction medium by other solvents failed (entries 4 and 5). In contrast to the palladium catalysis, *p*-benzoquinone (BQ) as catalytic redox mediator was not required (entry 6). When the alkenylation

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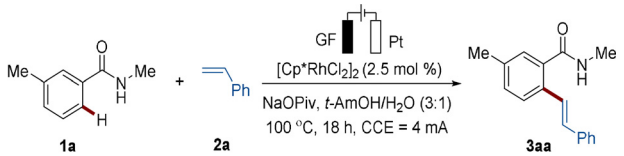
Table 1: Optimization of the rhodium-catalyzed C–H olefination.[a]



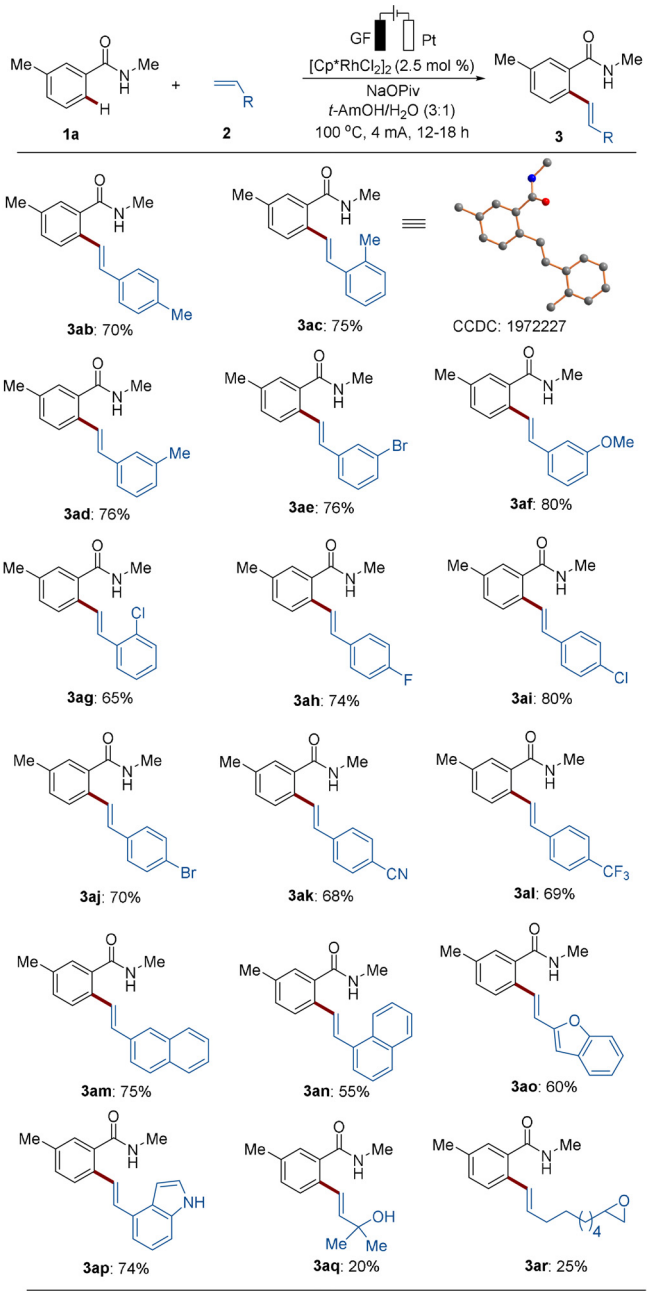
Entry	Deviation from standard conditions	Yield [%][b]
1	none	73
2	KOPiv instead of NaOPiv	54
3	NaOAc instead of NaOPiv	38
4	*i*-PrOH/H_2O (1:1)	trace
5	H_2O	trace
6	addition of TEMPO (0.1 equiv)	65
7	8 mA instead of 4 mA	60
8	80 °C, 30 h	40
9	$[Cp^*RhCl_2]_2$ (1.5 mol %)	50
10	1 mmol scale (4 mL solvent)	85
11	no electricity	trace
12	$Cu(OAc)_2$ (2.0 equiv) instead of electricity	0
13	$Pd(OAc)_2$ instead of $[Cp^*RhCl_2]_2$	0
14	$[Cp^*IrCl_2]_2$ instead of $[Cp^*RhCl_2]_2$	0

[a] Standard conditions: Undivided cell, GF anode, Pt cathode, constant current (CCE) = 4 mA, **1a** (0.4 mmol), **2a** (0.8 mmol), NaOPiv (0.8 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), *t*-AmOH/H_2O (4 mL), under air, 18 h. [b] Yield of isolated product.

reaction was performed on a 1 mmole scale, the product **3aa** was isolated in 85 % yield (entry 10). Control experiments confirmed the essential role of the electricity and the rhodium catalyst for the electrooxidative alkenylation (entries 11–14).

With the optimized reaction conditions in hand, we explored the scope of the electrochemical transformation. We first examined the C–H electroalkenylation with substituted alkenes **2** (Scheme 2). Independent of the electronic properties and positions of the substituents, a wide range of styrenes **2a**–**2n** efficiently underwent the intermolecular alkenylation to afford (*E*)-stilbenes **3** in good yields. The structure of product **3ac** was further confirmed by single-crystal X-ray analysis.[17a] Heteroaryl- and naphthyl-substituted alkenes were also compatible, and the expected products **3ao**–**3ap** were obtained in moderate to good yields. Alkyl-substituted terminal alkenes gave a minor amount of product. The alkenylation reaction was compatible with various sensitive functional groups, such as chloro, bromo, nitrile, and hydroxyl.

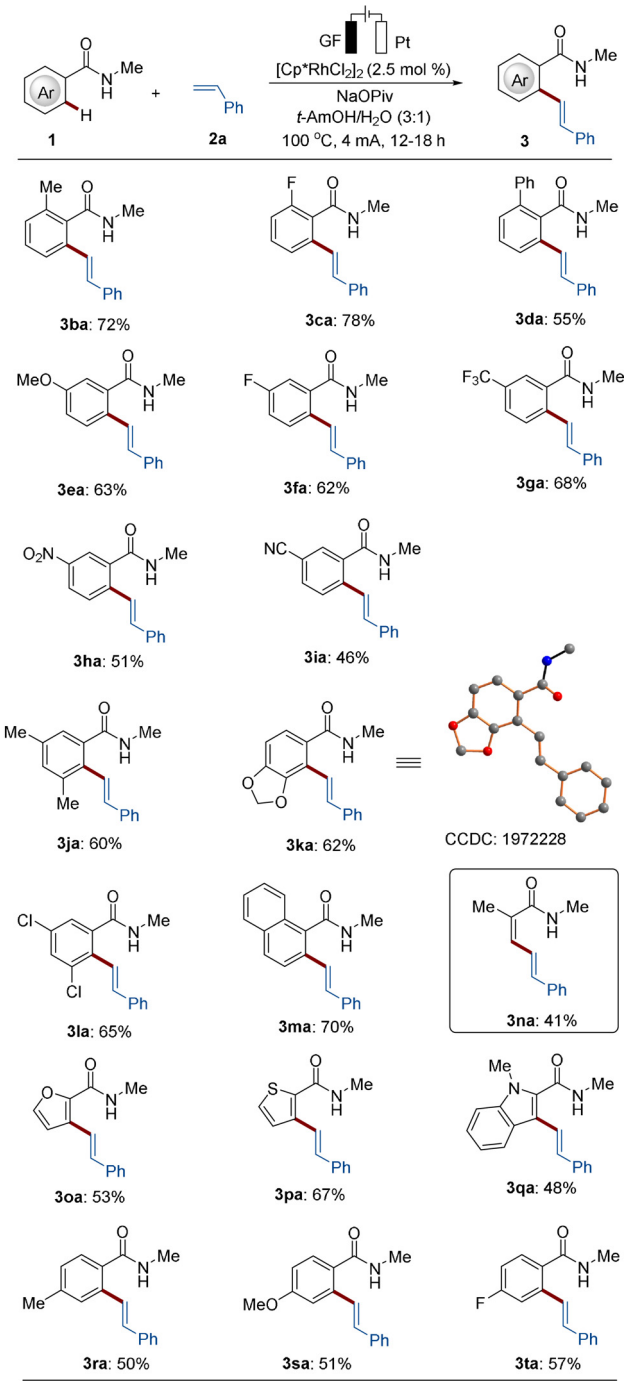
The scope of the alkenylation reaction was further examined with various substituted arenes **1** (Scheme 3). Generally, electron-donating as well as electron-withdrawing substituents on the benzamides **1** did not significantly alter the reaction efficiency and (*E*)-stilbenes **3** were selectively obtained (**3ea**–**3ja**). In addition, the steric hindrance of a substituent in the *ortho*-position was found to have a considerable impact on the reaction (**3ba**–**3da**). Interestingly, due to the dual coordination of an ether oxygen atom and a carbonyl oxygen atom in the reaction of substrate **1k** with **2a**, the alkenylation took place at the more sterically hindered C–H bond to deliver product **3ka**,[17b] which was consistent with earlier report.[18] It is noteworthy that α,β-unsaturated amides,[19] such as substrate **1n**, also reacted with



Scheme 2. Rhoda-electrocatalyzed C–H olefination with alkenes **2**.

styrene and the corresponding diene product **3na** was obtained. Heterocyclic amides, such as thiophene-3-carboxamide (**1p**) and indol-2-carboxamide (**1q**), were also applicable in this transformation to afford the corresponding products **3oa**–**3qa**. Additionally, when the alkenylation was tested with *para*-substituted symmetrical benzamides **1r**–**1t**, the corresponding products were obtained in moderate yield, along with minor amounts of the diolefinated products.

Next, we sought to examine various substitutions in the amide motif, considering diversity in both steric and electronic properties (Table 2). Indeed, the regioselectivity was improved with an increase in steric hindrance at the NH moiety, which can regulate the coordination to the rhodium center. These findings clearly showed that changing to

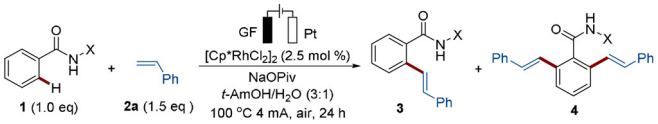


Scheme 3. Rhoda-electrocatalysis with benzamides **1**.

a longer *N*-alkyl group leads to lower conversion. Reactions could not be conducted with a secondary *N*-alkyl group or *N*-cycloalkyl benzamide. Thus, we propose that the *N*-methyl amide group is the best choice for this transformation (see Table S-4 for more details).

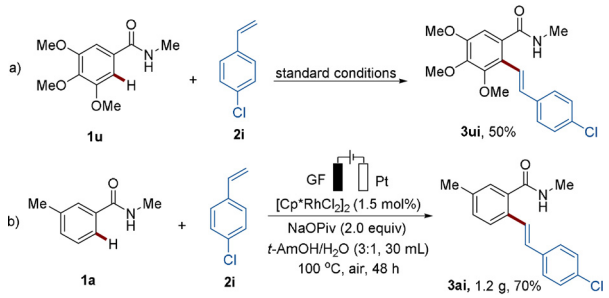
The optimized protocol was also applied to the conversion of 3,4,5-trimethoxybenamide (**1u**) to access the biologically relevant combretastatin A4 derivative **3ui**. The scalability of the C–H activation was also investigated and a 6 mmole scale reaction of **1a** and **2i** yielded 1.2 g of product **3i** with reduced catalyst loading (Scheme 4).

Table 2: Screening of the amide directing group.



Entry	X	**1**, recovered [%]	Ratio **3**/**4**[a]	**3**, yield [%][a]
1	H	**1v**, 20	2:1	**3va**, 34
2	Me	**1w**, 10	4:1	**3wa**, 64
3	Et	**1x**, 20	7:1	**3xa**, 60
4	*n*-Pr	**1y**, 41	8:1	**3ya**, 40
5[b]	*n*-Pr	**1y**, 5	1.1:1	**3ya**, 43
6	*i*-Pr	**1a′**, 96	–	0
7		**1b′**, 95	–	0
8	*t*-Bu	**1d′**, 99	–	0
9	Ts	**1f′**, 0	–	0
10	Ph	**1g′**, trace	–	trace

[a] Yield of isolated product. [b] 2.5 equiv **2a**.



Scheme 4. a) Combretastatin A4 analogue and b) gram-scale reaction.

To probe the reaction mechanism, we explored the electrochemical C–H activation by means of cyclic voltammetry (Figure 1 and Figures S1 and S2 in the Supporting Information). The addition of NaOPiv and the substrate **1a** led at a scan rate of 100 mV s^{-1} to an oxidation potential of $E_{p,ox} = 1.5$ V vs. SCE the Cp*Rh^{III} species. The modified substrates *N*-phenylacetamide **5** and *N*,*N*-dimethylbenzamide **6** with weakly coordinating oxygen[20a,b] gave no products and the starting materials were recovered (Scheme 5 a,b). Under the standard conditions, H/D exchange between amide **1a** and D_2O was observed in the presence of alkene **2a**, revealing significant deuteration in the recovered substrate **1a** (Scheme 5 c). Considering that this rhodium(III)-catalyzed electro-oxidative alkenylation includes a C–H activation step, a kinetic isotope effect (KIE) study was also conducted (Scheme 5 d). The intermolecular competition experiments provided a P_H/P_D value of 2.1 and parallel independent reactions resulted in a value of k_H/k_D of 1.1. These results indicate that the C–H cleavage is likely not the rate-determining step.[20c]

On the basis of our experimental results and related literature,[14a,b,d,21] a plausible catalytic cycle is presented for the rhodium(III)-catalyzed electrochemical C–H alkenylation. As depicted in Figure 2, coordination of the N-atom of amide **1a** to Cp*Rh^{III} and subsequent directed cyclorhodation at the *ortho*-position affords rhodacycle **A**. Then, alkene **2**

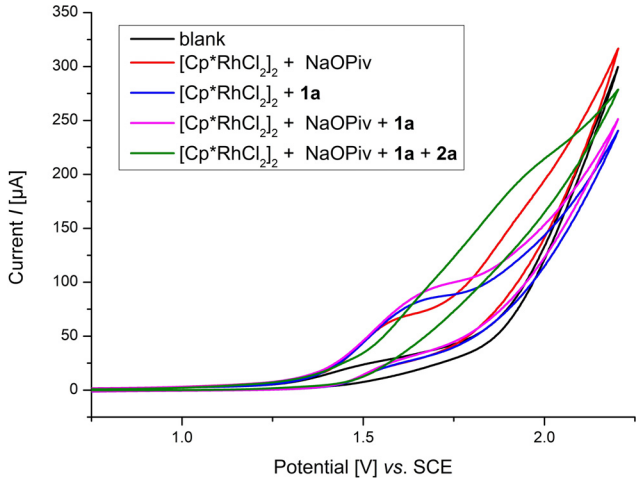
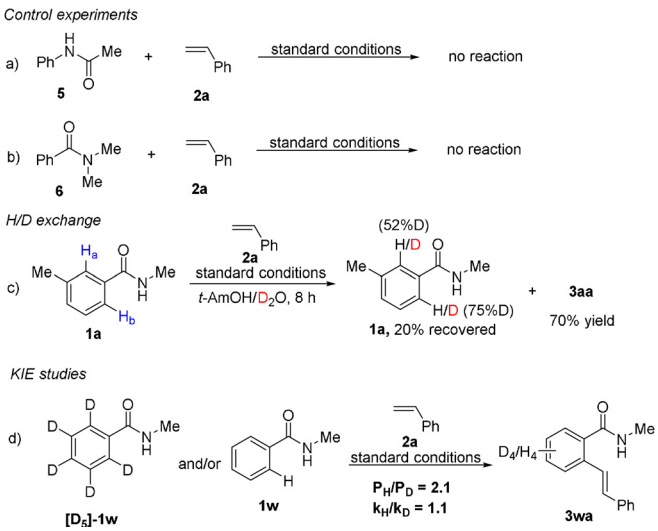


Figure 1. Cyclic voltammetry studies. Conditions: substrates (5 mmol L^{-1}), nBu$_4$NPF$_6$ (100 mmol L^{-1}), MeOH, 100 mV s^{-1}. Cyclic voltammograms of blank (black), [Cp*RhCl$_2$]$_2$ (2.5 mM) and NaOPiv (red), [Cp*RhCl$_2$]$_2$ (2.5 mM) and **1a** (blue), [Cp*RhCl$_2$]$_2$ (2.5 mM), NaOPiv, and **1a** (pink), [Cp*RhCl$_2$]$_2$ (2.5 mM), NaOPiv, **1a**, and **2a** (green).



Scheme 5. Summary of key mechanistic findings.

insertion occurs to give intermediate **B**, which undergoes β-hydrogen elimination to form **3** together with a rhodium(II) species, which is formed after dissociation of the N-atom in **C**. Finally, the rhodium(II) species is reoxidized to rhodium(III) at the anode, generating molecular hydrogen as the byproduct at the cathode and completing the catalytic cycle.

In conclusion, we have shown that benzamides, a common motif in natural products and drugs, are suitable substrates for selective and efficient rhodium(III)-catalyzed electrooxidative C–H olefination reactions using alkenes. Notably, both electron-poor and electron-rich styrenes were well tolerated as well as many sensitive functional groups, including bromo, hydroxyl, and nitro. Our observations have shown that the bulk of the alkyl group on the amide motif is a critical factor for achieving monoselectivities in high yields. Control experiments and H/D exchange studies were conducted and a plausible mechanism was proposed.

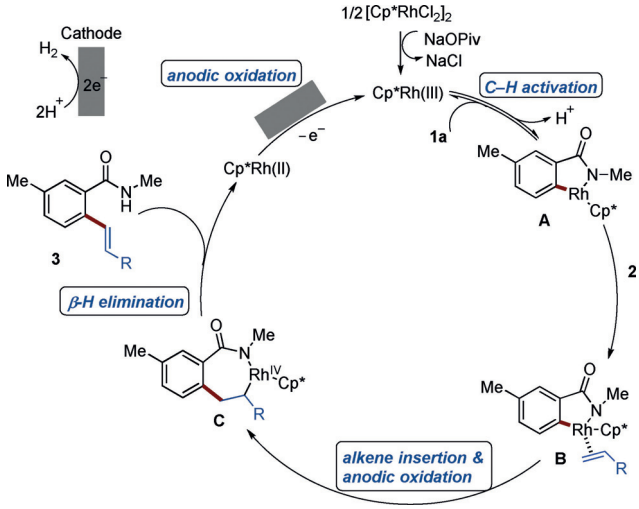


Figure 2. Proposed catalytic cycle.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · C–H alkenylation · electrochemistry · olefination · rhodium

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