

Rhoda-Electrocatalyzed C–H Methylation and Paired Electrochemical C–H Ethylation and Propylation

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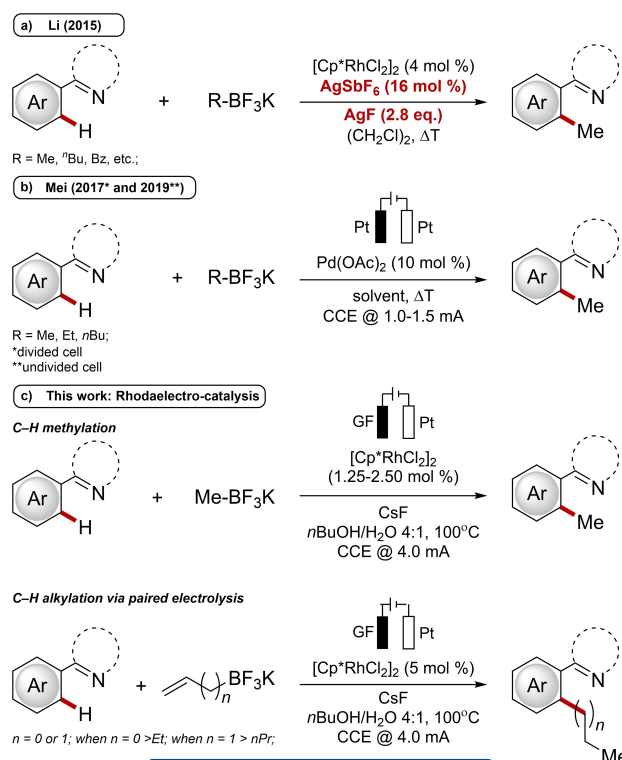
Abstract: The use of electricity over traditional stoichiometric oxidants is a promising strategy for sustainable molecular assembly. Herein, we describe the rhoda-electrocatalyzed C–H activation/alkylation of several *N*-heteroarenes. This catalytic approach has been successfully applied to several

arenes, including biologically relevant purines, diazepam, and amino acids. The versatile C–H alkylation featured water as a co-solvent and user-friendly trifluoroborates as alkylating agents. Finally, the rhoda-electrocatalysis with unsaturated organotrifluoroborates proceeded by paired electrolysis.

Sustainable and eco-friendly organic approaches proceeded by the electrocatalysis have gained recent significant attention,^[1] especially due to the fact that electric current can be employed as waste-free redox equivalent, and thus preventing the use of expensive and frequently toxic chemical oxidants.^[2] The combination of electrochemistry with transition-metal-catalyzed C–H activations aspires to be one of the most desired strategies in modern organic transformations.^[3,4] However, the paired electrolysis manifolds are still in their infancy.^[5]

Among numerous types of functionalization, the late-stage incorporation of simple alkyl groups (such as methyl or ethyl groups) plays a specific role in the modulation of biorelevant molecules.^[6] The so-called “magic methyl effect” determines a significant boost in the potency of several biologically active compounds.^[7] Consequently, a direct C–H methylation arguably represents an important strategy.^[8] Among these, Li developed a rhodium-catalyzed approach utilizing silver salt as the oxidant (Scheme 1a).^[8] To the best of our knowledge, there are only two examples with organoborons reported by the Mei group on palladium-catalyzed electrochemical C–H alkylation of oxime ethers and 2-phenylpyridines (Scheme 1b).^[10]

Within our program on metalla-electrochemical C–H activation,^[4e] we wondered whether rhoda-electrocatalyzed C–H methylation would be viable. To prove our hypothesis, we examined electrocatalysis for the metalla-mediated replacement



**Electrocatalytic C–H Alkylation
Electricity as Green Oxidant
Various *N*-Heterocycles
H₂O-Tolerant Protocol
Paired Electrolysis**

Scheme 1. Strategies for catalyzed C–H alkylation.

of C–H bonds by C–CH₃ in variously substituted *N*-heteroarenes (Scheme 1c, top). Thereby, we also discovered an unprecedented rhodium-catalyzed electro-oxidative olefination combined with the in situ reduction of the C–C double bond through the use of vinyl and allyl trifluoroborates (Scheme 1c, bottom). Salient features of our strategy comprise (a) methylation through versatile rhodium catalysis, (b) a user-friendly undivided cell setup, (c) no additional electrolyte, (d) efficient

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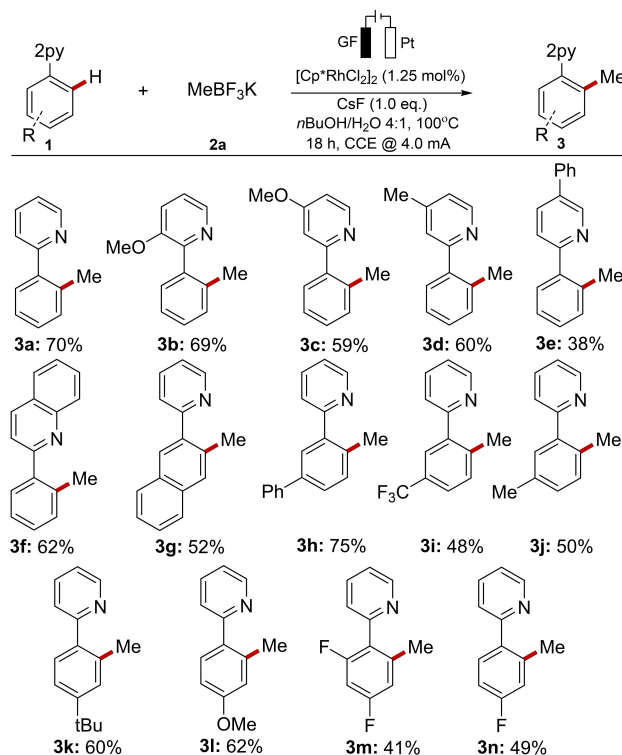
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transformation of several *N*-heteroarenes including biologically relevant amino acids and purines, and (e) unprecedented rhoda-electrocatalyzed alkylation through in situ reduction as an example of paired electrolysis approach.

We initiated our alkylation studies by examining a wide range of commercially available transition metal complexes, methylating agents, and additives, using a user-friendly undivided cell setup (Table 1 and Table S1 in the Supporting Information). After considerable experimentation, we found that the C–H methylation of arene **1a** with potassium methyltrifluoroborate (**2a**) in the presence of [Cp*RhCl₂]₂ (1.25 mol%), and CsF in *n*BuOH/H₂O mixture (4:1) delivered product **3a** with 70% isolated yield (Table 1, entry 1). Control experiments showed that other transition metal complexes were mostly inactive in this transformation (Table 1, entries 4–8; Table S1), and the essential role of the rhodium catalyst was also confirmed (Table 1, entry 4). We also demonstrated the necessity of electricity (Table 1, entry 2), and that caesium fluoride was the additive of choice (although other additives were only slightly less efficient; Table 1, entries 8–9). Attempts to replace the alkylating source with other methyl organoborons gave inferior results (Table 1, entries 10–11).

With the optimized conditions in hand, we investigated the scope of the *sp*² C–H methylation (Scheme 2). Electron-rich, as well as electron-deficient 2-phenylpyridines **1a–1n** were ame-



Scheme 2. Rhoda-electrocatalyzed C–H methylation of arylpyridines **1**.

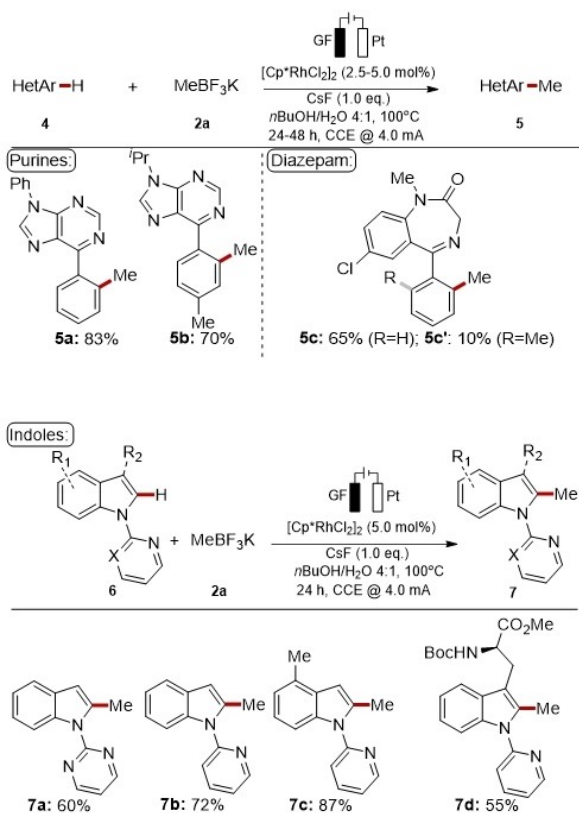
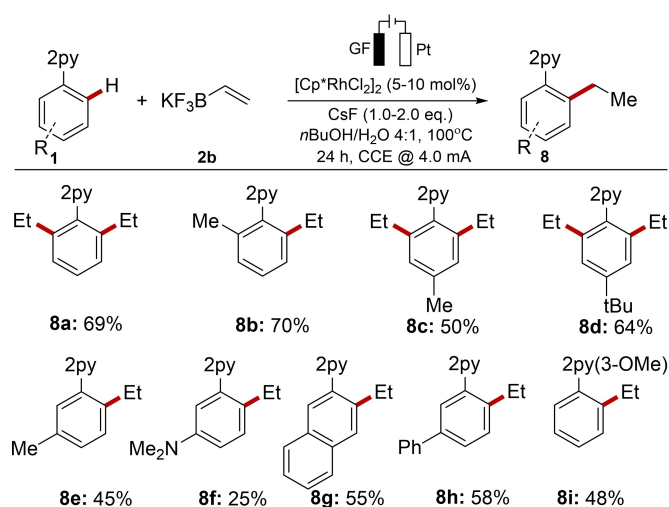
Table 1. Optimization of metalla-electrocatalyzed C–H methylation.^[a]

| Entry | Variation from standard conditions | Ratio [3a:3a'] | Yield of 3a [%] ^[b] |
|-------------------|--|----------------|--------------------------------|
| 1 | no change | 9:1 | 72 (70) |
| 2 | no electricity | 9:1 | 12 ^[c] |
| 3 | under N ₂ atmosphere | 10:1 | 55 |
| 4 | no catalyst | – | NR |
| 5 | [Cp*Co(CO) ₂] ₂ instead of [Cp*RhCl ₂] ₂ | – | NR |
| 6 | RhCl ₃ ·3H ₂ O instead of [Cp*RhCl ₂] ₂ | – | NR |
| 7 | [RhCl(COD)] ₂ instead of [Cp*RhCl ₂] ₂ | – | traces |
| 8 | [Cp*IrCl ₂] ₂ instead of [Cp*RhCl ₂] ₂ | – | traces |
| 9 | NaOPiv instead of CsF | 9:1 | 68 (62) |
| 10 | <i>n</i> Bu ₄ NPF ₆ instead of CsF | 9:1 | 60 (55) |
| 11 ^[d] | 3.0 equiv. of trimethylboroxine instead of MeBF ₃ K | 9:1 | 65 |
| 12 | 3.0 equiv. of MeB(OH) ₂ instead of MeBF ₃ K | 9:1 | 41 |
| 13 | 6.0 mA instead of 4.0 mA | 7:1 | 57 |
| 14 | 2.0 mA instead of 4.0 mA | 9:1 | 60 |
| 15 | <i>t</i> AmOH/H ₂ O 4:1 | 9:1 | 68 (61) |
| 16 | 1 mol% of [Cp*RhCl ₂] ₂ | 9:1 | 52 |
| 17 | 2.5 mol% of [Cp*RhCl ₂] ₂ | 9:1 | 70 |

[a] General reaction conditions: Undivided cell, graphite felt anode, Pt cathode, constant current (CCE)=4.0 mA, **1a** (0.25 mmol), **2a** (0.75 mmol), CsF (0.25 mmol), [Cp*RhCl₂]₂ (1.25 mol%), under air atmosphere, 18 h; Current density = 2.67 mA/cm²; Faradaic Efficiency = 13.4%. [b] NMR Yield determined with trimethoxybenzene as the internal standard. Isolated yield in parenthesis. [c] Under air atmosphere. [d] Nominally 9.0 eq. of methyl groups.

nable to the rhodium-catalyzed electrocatalysis, and the desired products **3a–3n** were selectively obtained (up to 75%). We also probed the robustness of the electrocatalysis by employing more challenging purines. Thus, the purines were selectively mono-*ortho*-methylated (Scheme 3). To our delight, the electrocatalyzed C–H methylation proceeded smoothly and gave the mono- and dimethylated diazepames **5c/5c'** in good, isolated yield (65% (mono), 10% (di), Scheme 3). Furthermore, we found that substituted indoles were also competent substrates (**6a–6c**), providing the corresponding products with high positional-selectivity. Likewise, tryptophan (**6d**) was successfully methylated under electrocatalysis (**7d**), highlighting a notable potential for late-stage diversification (Scheme 3).

Given the success of the electrocatalyzed C–H methylation, we wondered whether other C–H alkylation would be viable. In this context, we discovered that potassium vinyltrifluoroborate (**2b**) with [Cp*RhCl₂]₂ (5 mol%) as the catalyst, and CsF as an additive, delivered the ethylated product **8b** in 70% (Scheme 4). Interestingly, both NMR and HRMS analysis confirmed the formation of the unexpected, ethylated derivative. Thus, we examined a wide range of reaction conditions (Table 2, Table S2). Preliminary experimentation indicated that [Cp*RhCl₂]₂ was the optimal catalyst (Table 2, entries 5–7; Table S2). Moreover, caesium fluoride was again slightly more effective than other additives (Table 2, entries 8–9; Table S2). Critical to the success of this reaction was the use of electricity (Table 2, entry 2), as well as the utilization of *n*BuOH and H₂O as the medium (Table S2).

Scheme 3. Rhoda-electrocatalyzed C–H methylation of *N*-heterocycles.

Scheme 4. Rhoda-electrocatalyzed C–H ethylation of 2-phenylpyridines.

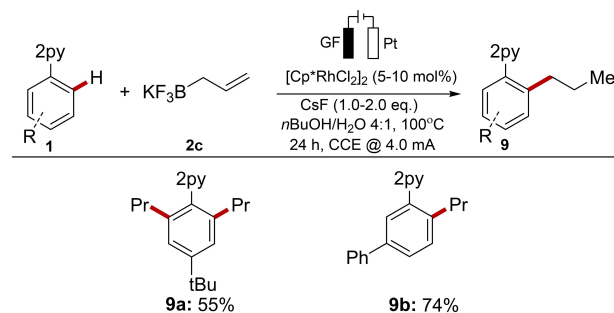
Next, we set out to investigate the scope of this unprecedented rhoda-electrocatalyzed paired vinylation/reduction (Scheme 4). Notably, 2-phenylpyridines without steric hindrance gave equimolar amounts of mono- and dialkylated product. Therefore, here, stoichiometry was adjusted. Furthermore, potassium allyltrifluoroborate (**2c**) was also effective, leading to propylated products **9a** and **9b** (Scheme 5). Next, the generality of this method with respect to the purines and

Table 2. Optimization of the rhoda-electrocatalyzed C–H ethylation.^[a]

1p + 2b $\xrightarrow{[Cp^*RhCl_2]_2 (5 \text{ mol}\%), CsF (1.0 \text{ eq.}), nBuOH/H_2O 4:1, 100^\circ C, 24 \text{ h, CCE @ 4.0 mA}}$ 8b

| Entry | Variation from standard conditions | Yield of 8b [%] ^[b] |
|-------|--|---------------------------------------|
| 1 | no change | 72 (70) |
| 2 | no electricity | traces |
| 3 | under N ₂ atmosphere | 59 |
| 4 | in divided cell system ^[c] | 55 |
| 5 | no catalyst | NR |
| 6 | [RuCl ₂ (<i>p</i> -cym) ₂ instead of [Cp*RhCl ₂] ₂ | traces |
| 7 | RhCl ₃ ·3H ₂ O instead of [Cp*RhCl ₂] ₂ | NR |
| 8 | NaOPiv instead of CsF | 66 (62) |
| 9 | <i>n</i> Bu ₄ NPF ₆ instead of CsF | 65 |
| 10 | <i>t</i> AmOH/H ₂ O 4:1 | 70 (66) |
| 11 | 2.5 mol % of [Cp*RhCl ₂] ₂ | 22 |

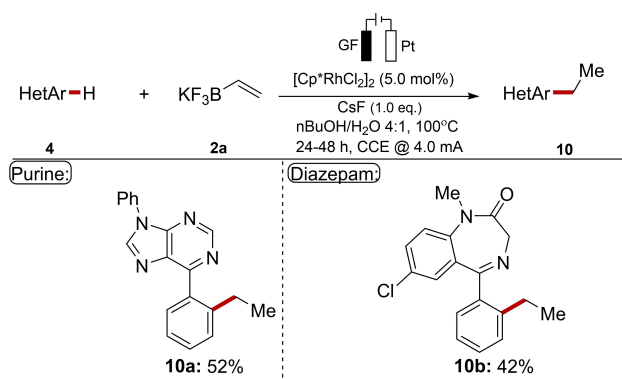
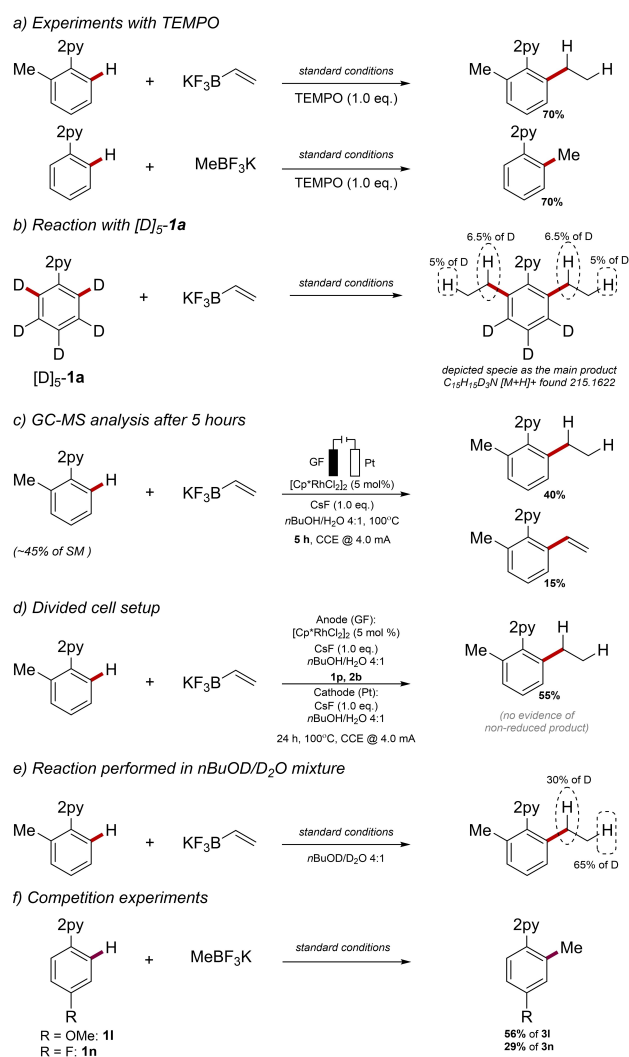
[a] General reaction conditions: Undivided cell, graphite felt anode, Pt cathode, constant current (CCE) = 4.0 mA, **1p** (0.25 mmol), **2b** (0.75 mmol), CsF (0.25 mmol), [Cp*RhCl₂]₂ (5 mol%), under air atmosphere, 24 h. [b] NMR Yield determined with trimethoxybenzene as the internal standard. Isolated yield in the parenthesis. [c] Divided cell, GF anode, Pt cathode, constant current (CCE) = 4.0 mA; Anode part: **1p** (0.25 mmol), **2b** (0.75 mmol), CsF (0.25 mmol), [Cp*RhCl₂]₂ (5 mol%), *n*BuOH/H₂O 4:1; Cathode part: CsF (0.25 mmol), *n*BuOH/H₂O 4:1.



Scheme 5. Rhoda-electrocatalyzed C–H propylation of 2-phenylpyridines

diazepam was also explored. Both were shown to be suitable substrates for this transformation, displaying high *mono*-selectivity (Scheme 6).

To gain mechanistic insights into these rhoda-electrocatalyzed reactions, we conducted preliminary experiments. The alkylations were performed in the presence of typical radical scavengers such as TEMPO (Scheme 7a), leading the desired products (with the same efficiency), thereby implying that radical pathways were likely, not operative. Subsequently, we have focused primarily on the paired vinylation/reduction. The reaction conducted with isotopically labeled [D]₅-**1a** led to insignificant incorporation of deuterium into the final product, thus excluding a hydroarylation pathway (Scheme 7b). Then, we performed the tests to determine the source of hydrogen responsible for the reduction of the double bond. When the reaction was stopped after 5 h, GC analysis confirmed the formation of the vinylated product. Next, we used a divided cell setup to confirm the reduction by dihydrogen (Scheme 7d).

Scheme 6. Rhoda-electrocatalyzed C–H ethylation of *N*-heterocycles.

Scheme 7. Mechanistic studies on rhoda-electrocatalyzed C–H alkylation.

Notably, a reduced product was again observed as the only derivative. Furthermore, the reaction performed in *n*BuOD/*D*₂O mixture indicated the incorporation of one hydrogen atom as coming from a water molecule (Scheme 7e).

Finally, we performed an intermolecular competition experiment for the C–H methylation of two differently *para*-substituted 2-phenylpyridines (Scheme 7f). Thus, the electron-rich substrate proved to be superior.

On the basis of our experimental results, a plausible catalytic cycle is presented for the paired rhoda-electrocatalyzed C–H alkylation (Figure 1). Firstly, cyclo-rhodation at the *ortho*-position affords rhodacycle.^[11] Then, the transmetalation with VinBF_3K leads to the formation of a metallacyclic vinyl complex. Next, the reductive elimination occurs via a high-valent pathway (oxidatively induced reductive elimination)^[12] which finally provides C–H vinylated product. Furthermore, a subsequent reduction takes place to afford the ethylated product **3**.

In conclusion, we have developed chelation-assisted rhoda-electrocatalyzed C–H alkylations. The application to the late-stage functionalization has also been shown by performing facile alkylation of purines/amino acids. Finally, the rhoda-electrocatalysis with unsaturated organotrifluoroborates proceeded by paired electrolysis.

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Conflict of Interest

The authors declare no conflict of interest.

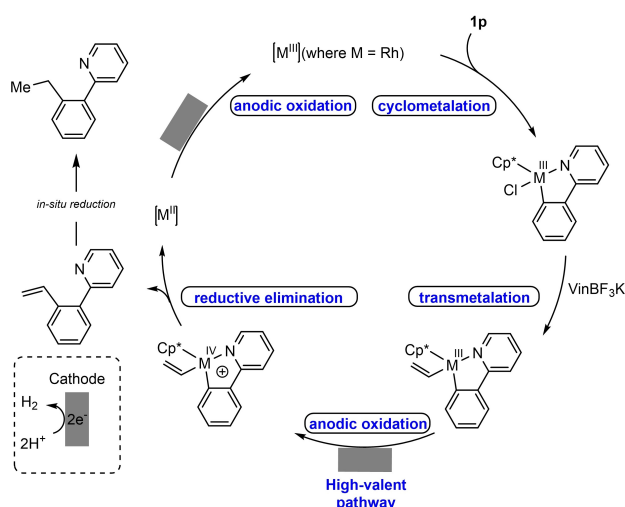


Figure 1. Proposed catalytic cycle.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: C–H activation · electrochemistry · methylation · paired electrolysis · rhodium

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