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Compartmentalization is a viable approach of ensuring the turnover of a solution cascade reaction with ephemeral intermediates, which may otherwise deactivate in the bulk solution. In biochemistry or enzyme-relevant cascade reactions, extensive models have been constructed to quantitatively analyze the efficacy of compartmentalization. Nonetheless, the application of compartmentalization and its quantitative analysis in non-biochemical reactions is seldomly performed, leaving much uncertainty about whether compartmentalization remains effective for non-biochemical, such as organometallic, cascade reactions.

Here, we report our exemplary efficacy analysis of compartmentalization in our previously reported cascade reaction for ambient CH4-to-CH3OH conversion, mediated by O2-deactivating RhII metalloradical with O2 as the terminal oxidant in Si nanowire array electrode. We experimentally identified and quantified the productivity of key reaction intermediates, including RhII metalloradical and reactive oxygen species (ROS) from O2. We subsequently determined that the nanowire array enables about 81 % of the generated ephemeral intermediate in air, RhII metalloradical, to be utilized towards CH3OH formation, which is 0% in homogenous solution. Such an experimentally determined value was satisfactorily consistent with the results from our semi-quantitative kinetic model. The consistency suggests that the reported CH4-to-CH3OH conversion surprisingly possesses minimal unforeseen side reactions, and is favorably efficient as a compartmentalized cascade reaction. Our quantitative evaluation of the reaction efficacy offers design insights and caveats into application of nanomaterials to achieve a spatially controlled organometallic cascade reactions.
Efficacy analysis of compartmentalization for ambient CH$_4$ activation mediated by Rh$^{II}$ metalloradical in nanowire array electrode

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Abstract: Compartmentalization is a viable approach of ensuring the turnover of a solution cascade reaction with ephemeral intermediates, which may otherwise deactivate in the bulk solution. In biochemistry or enzyme-relevant cascade reactions, extensive models have been constructed to quantitatively analyze the efficacy of compartmentalization. Nonetheless, the application of compartmentalization and its quantitative analysis in non-biochemical reactions is seldomly performed, leaving much uncertainty about whether compartmentalization remains effective for non-biochemical, such as organometallic, cascade reactions. Here, we report our exemplary efficacy analysis of compartmentalization in our previously reported cascade reaction for ambient CH$_4$-to-CH$_3$OH conversion, mediated by O$_2$-deactivating Rh$^{II}$ metalloradical with O$_2$ as the terminal oxidant in Si nanowire array electrode. We experimentally identified and quantified the productivity of key reaction intermediates, including Rh$^{II}$ metalloradical and reactive oxygen species (ROS) from O$_2$. We subsequently determined that the nanowire array enables about 81% of the generated ephemeral intermediate in air, Rh$^{II}$ metalloradical, to be utilized towards CH$_3$OH formation, which is 0% in homogenous solution. Such an experimentally determined value was satisfactorily consistent with the results from our semi-quantitative kinetic model. The consistency suggests that the reported CH$_4$-to-CH$_3$OH conversion surprisingly possesses minimal unforeseen side reactions, and is favorably efficient as a compartmentalized cascade reaction. Our quantitative evaluation of the reaction efficacy offers design insights and caveats into application of nanomaterials to achieve a spatially controlled organometallic cascade reactions.
INTRODUCTION

Compartmentalization, ubiquitous in biology, allows efficient transfer of reaction intermediary or ephemeral species within a multienzyme cascade reaction in the intracellular medium.\textsuperscript{1-3} By segregating subsequent catalytic sites from bulk environment at microscopic or even nanoscopic level, spatial control of catalytic reactions ensures the functionality of biological metabolism in a factory-like manner with high efficiency.\textsuperscript{4-6} Here the key to a successful compartmentalized cascade reaction is the capability of confining transient intermediate within the compartment and preventing its outflux that leads to either intermediate’s loss or deactivation (Figure 1A). A number of theoretical models have been established to evaluate the capability of compartmentalized cascade reactions in fulfilling this task\textsuperscript{7, 8}, predominantly in the context of enzymatic catalytic reactions.\textsuperscript{9-13} Reaction efficiency ($\gamma$), defined as the ratio between the product outflux and the substrate influx to the compartment for a one-to-one stoichiometric reaction (Figure 1A), quantitatively measures the efficacy of a cascade system in retaining and utilizing the intermediate species generated within the compartment.\textsuperscript{6, 9, 14, 15} With the value of $\gamma$ commonly approaching unity for cascade reactions in biology,\textsuperscript{4-6, 14} nature masters the design strategy of compartmentalization for enzymatic reactions.

The benefits of confining catalytic reactions spatially at microscopic and nanoscopic level in nature inspire the development of other non-enzymatic cascade, mostly with surface-attached molecular, nanoparticle, or enzyme catalysts in porous medium such as metal-organic frameworks\textsuperscript{16-18} or superposed on scaffolds\textsuperscript{10-12}. Nonetheless, analyzing and determining the value of $\gamma$, a quantitative figure-of-merit for the efficacy of compartmentalization, remains infrequent, to say the least, for non-enzymatic scenarios. As resonated in recent publications\textsuperscript{9, 16, 19}, the scarcity of experimentally determined $\gamma$ values casts uncertainty about the effectiveness of a certain design strategy of compartmentalization. A synergistic study comparing experimentally determined $\gamma$ values with the one from a theoretical model will offer valuable insights whether the designed cascade reaction is effective without undesirable side effects, ascertain the merits of designed compartmentalization, and further justify the design strategy of non-enzymatic compartmentalized systems. This research report aims to offer an exemplary case of such study for organometallic catalysis with compartmentalized systems.
We are interested in employing microscopic concentration gradients within nanomaterials to design organometallic catalytic cycles of seemingly incompatible steps, in which key reaction intermediates will be quickly deactivated once they diffuse out of the nanomaterials. In our previous report, a cascade catalysis with O$_2$-sensitive reaction intermediate was established to achieve ambient CH$_4$-to-CH$_3$OH conversion with O$_2$ as the terminal oxidant assisted with electricity. As shown in Figure 1B, nanowire array electrode electrochemically reduces rhodium (III) tetramesityl porphyrin iodide (Rh$^{III}$) into rhodium (II) tetramesityl porphyrin metalloradical (Rh$^{II}$) in aprotic solvent 1,2-difluorobenzene (1,2-DFB). At the same time, the nanowire array reduces O$_2$ into reactive oxygen species (ROS) and creates a sharp O$_2$ concentration gradient with
a locally O$_2$-free environment near the bottom of nanowire array in aerobic conditions. In the O$_2$-free microenvironment, two equivalents of the generated Rh$^{	ext{III}}$ species, while highly reactive with O$_2$, activate one equivalent of CH$_4$ ambiently to yield methylated rhodium (III) tetramesityl porphyrin (Rh$^{	ext{III}}$-CH$_3$) and rhodium (III) tetramesityl porphyrin hydride (Rh$^{	ext{III}}$-H). Both species are proposed to react with the generated ROS that remain to be further identified (vide infra), leading to the formation of CH$_3$OH. While no barrier is present to physically separate the liquid phase within the nanowire array from the bulk solution, the whole system can be considered as a compartmentalized cascade with the nanowire array as the compartment with its unique microenvironment (Figure 1C), analogous to the previous argument in the case of two-enzyme cascades in which enzymes are placed in close proximity at nano-scale. The overall process was reported to be catalytic, achieving turnover number up to 52,000 within 24 hours. The synergy between nanomaterials and organometallic chemistry warrants a new catalytic route of CH$_4$ functionalization, while additional study is needed to understand the underlying mechanism and quantitatively evaluate the efficacy of the strategy that interface nanowires with organometallics.

Here we report our analysis of the above-mentioned CH$_4$-to-CH$_3$OH catalysis in the context of compartmentalized cascade. We translated the reported catalytic system into a theoretical model that estimates the numerical value of $\gamma$. Electron paramagnetic resonance (EPR) spectroscopy with spin-trap agent, along with other characterizations, unraveled that the predominant ROS present in the system is superoxide and illustrated its role in CH$_3$OH formation. This piece of mechanistic insight allowed us to subsequently determined the value of $\gamma$ in the catalysis, which surprisingly amounts to more than 80%. The high value of measured $\gamma$ is consistent with our theoretical framework and illustrates the efficacy of the created nanoscopic concentration gradient with minimal side reactions. Our results demonstrate that carefully designed compartmentalization, spatially controlling the occurrence of organometallic reactions in solution at microscopic length scale, can circumvent undesirable reactions efficiently and create organometallic catalytic cycles impossible in homogenous solution.

**RESULTS AND DISCUSSION**

**A theoretical framework of cascade reactions in nanowire array electrode**
Generally applicable for non-enzymatic cascade design as noted above, one question that we ask is whether our previously reported design employing nanowire array and concentration gradient is effective in utilizing the ephemeral $O_2$-sensitive intermediates $\text{Rh}^{\text{II}}$, whose activation of $\text{CH}_4$ was considered turnover-limiting.\textsuperscript{20, 24} Our approach to this question is to construct a numerical model in the context of compartmentalization and analyze the reaction efficiency $\gamma$ that will be valuable for future design consideration. Figure 1C displays the reported reaction in the context of compartmentalized cascade reactions. Here the compartment, schematically shown as a yellow-colored dashed box, is defined as the $O_2$-free liquid phase within the nanowire array where $\text{Rh}^{\text{II}}$-initiated $\text{CH}_4$ activation is proposed to take place. Following its definition\textsuperscript{9, 15}, $\gamma$ is expressed as the ratio between the outward flux of $\text{Rh}^{\text{II}}$−$\text{CH}_3$ for $\text{CH}_3\text{OH}$ formation ($R_p$) and the rate of $\text{Rh}^{\text{II}}$ generation ($R_s$) during the electrolysis. Based on the proposed reaction mechanism (Figure 1B and 1C), $R_p$ and $R_s$ are dictated by the kinetic rate constant of electrochemical reduction of $\text{Rh}^{\text{III}}$ into $\text{Rh}^{\text{II}}$ ($k_1$) as well as the $\text{Rh}^{\text{II}}$-initiated $\text{CH}_4$ activation ($k_2$), respectively. We note that $\gamma$ could also be interpreted as the competition between the rate of $\text{CH}_4$ activation ($R_p$) in the compartment and the deactivation of $\text{Rh}^{\text{II}}$ with $O_2$ in the bulk, whose rate constant is denoted as $k_c$. Because such a competition depends on the diffusive mass transport at steady state, another important factor is the diffusive conductance $F$, as used in the design of enzymatic cascades\textsuperscript{6, 9, 13}, which describes the rate of mass transport for chemical species crossing into and out of the compartment boundary. However, in order to obtain the flux of a particular species in and out of the compartment, $F$ must be normalized to the volume of the compartment $V$ and Avogadro’s number $N_A$.\textsuperscript{9} We anticipate that $F$ and $V$ will be co-dependent, therefore we derive an expression for $F/(VN_A)$, denoted $F_V$, in terms of nanowire geometry (Section 1A of the Supplementary Information). Since $\text{Rh}^{\text{II}}$, $\text{Rh}^{\text{III}}$, and $\text{Rh}^{\text{III}}$−$\text{CH}_3$ species share the bulky metalloporphyrin structure, as a first-order approximation $F_V$ is assumed to be the same among $\text{Rh}^{\text{II}}$, $\text{Rh}^{\text{III}}$, and $\text{Rh}^{\text{III}}$−$\text{CH}_3$, and only dependent on the morphology of the nanowire array. Assuming $k_c \to \infty$ due to the reported rapid deactivation\textsuperscript{21}, we incorporated the above-mentioned components and derived a numerical model (Sections 1B of the Supplementary Information), which describes $\gamma$ in compartmentalized cascade as shown below:

$$\gamma = \frac{R_p}{R_s} = \frac{k_1 F_V C_{\text{Rh.total}}}{k_2 (F_V + k_1) [\text{Rh}^{\text{II}}]^2 C_{\text{CH}_4}}$$  \hspace{1cm} (1)$$

$$F_V \approx \frac{8D}{L^2}$$  \hspace{1cm} (2)
Here $C_{\text{Rh,total}}$ is the total concentration of Rh species in the bulk solution, almost exclusively in the form of Rh$^{\text{III}}$, $[\text{Rh}^{\text{II}}]$ the steady-state concentration of Rh$^{\text{II}}$ in the compartment during electrolysis that remains to be numerically calculated; $C_{\text{CH}_4}$ the concentration of CH$_4$ in the bulk solution; $D$ the diffusion coefficient of Rh species; and $L$ the length of nanowire array. Similarly, we derived the expression of $\gamma$ in the non-compartmentalized homogenous solution (Section 1C of the Supplementary Information). After solving the steady-state kinetic equations that include the mass transport across the compartment, we further derived the expressions of $\gamma$ from equation (1) for nanowire array electrode:

$$\gamma = \frac{(FV + k_1) \left( -FV + \sqrt{FV^2 + \frac{4FVk_1k_2C_{\text{CH}_4}C_{\text{Rh,total}}}{FV + k_1}} \right)^2}{4FVk_1k_2C_{\text{CH}_4}C_{\text{Rh,total}}} \quad (3)$$

And the expressions of $\gamma$ in a homogenous solution:

$$\gamma' = \frac{\left( -k_e + \sqrt{k_e^2 + 4k_1k_2C_{\text{CH}_4}C_{\text{Rh,total}}} \right)^2}{4k_1k_2C_{\text{CH}_4}C_{\text{Rh,total}}} \quad (4)$$

We note that $k_e$ is explicitly incorporated in equation (4) while we assumed $k_e \rightarrow \infty$ in equation (3). The above equations establish the theoretical framework for us to analyze the efficacy of the organometallic reactions in the nanowire array electrode.

The established theoretical model demands input from experimental results. Because of the high reactivity between Rh$^{\text{II}}$ and O$_2$ outside of the O$_2$-free microenvironment in the nanowire array$^{21}$, i.e. $k_e \rightarrow \infty$, $\gamma$ can be approximated as the ratio between the amount of generated CH$_3$OH ($N_{\text{CH}_3\text{OH}}$) and Rh$^{\text{II}}$ from electrochemical reduction of Rh$^{\text{III}}$ ($N_{\text{Rh(II)}}$) (Figure 1C), if we presume that the conversion from Rh$^{\text{III}}$–CH$_3$ to CH$_3$OH is stoichiometric as corroborated by our prior experimental evidence.$^{20}$ While $N_{\text{CH}_3\text{OH}}$ is experimentally readily measurable as we have done before$^{20}$, the value of $N_{\text{Rh(II)}}$ is less accessible and requires the quantification of ROS because the electrochemical reduction of Rh$^{\text{III}}$ into Rh$^{\text{II}}$ is concurrent with the electrochemical reduction of O$_2$ into ROS (Figure 1B). Therefore, identification and quantification of the ROS in this catalytic system is needed, not only for deeper insights about the chemical steps involved in the catalysis but also for a quantitative determination of $\gamma$. 
Identification and quantification of reactive oxygen species in the catalysis

The identity of predominant ROS was probed by EPR spectroscopy with the addition of spin trap agent 5,5-dimethyl-1-pyrroline N-oxide (DMPO) during the electrolysis. Superoxide (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and hydroxyl radical (•OH) were presumed to be the possible ROS from O$_2$ reduction in aprotic solvent systems. Among those possible ROS, H$_2$O$_2$, along with other hydroperoxide species, react with DMPO to yield the adduct DMPO–OH•, which can be detected by EPR spectroscopy. While O$_2^-$ and •OH are short-lived, their reactions with DMPO yield more stable adducts DMPO–O$_2^-$ and DMPO–OH•, whose prolonged lifetimes are roughly 1 and 20 minutes, respectively, at room temperature and much longer at liquid N$_2$ condition. By trapping the generated ROS with DMPO during the electrolysis and discerning the trapped radicals in EPR spectroscopy the possible presence of O$_2^-$ and H$_2$O$_2$/•OH could be unveiled.

EPR spectra indicate that O$_2^-$ is the predominant ROS during the CH$_4$-to-CH$_3$OH conversion. As reported in our previous work (Section 3A in Supplementary Information), CH$_4$-to-CH$_3$OH catalysis was conducted in a customized single-chamber electrochemical reactor (Figure S1), which was fed by a mixture of CH$_4$ and air ($P_{CH4}/P_{air} = 35$) at a constant flow rate at ambient pressure and room temperature. Chronoamperometry of $-1.4$ V vs. Saturated Calomel Electrode (SCE) was applied in 1,2-DFB with 1 mM of Rh$^{	ext{III}}$ as pre-catalyst and 0.1 M tetrabutylammonium perchlorate (TBAClO$_4$) as supporting electrolyte. Si nanowire array with average wire length of 15 µm and diameter of 50 nm (Figure S2), prepared based on literature, was used as the working electrode with a Pt wire counter electrode and a Ag$^+/Ag$ pseudo-reference electrode equipped with a glass frit. 50 mM DMPO was added during the electrolysis to trap the generated ROS, and aliquots were taken for EPR experiments 5, 15, and 60 minutes after the addition of DMPO. Unless stated specifically, the aliquots were stored in liquid N$_2$ before EPR measurement, although the DMPO adduct has been observed to be stable at room temperature for at least 90 minutes (Figure S3). We note that the addition of DMPO per se does not significantly alter the electrochemistry in the system, if any, because previous study has shown that DMPO is cathodically stable up to $-2.35$ V vs. SCE. The EPR spectrum from the aliquot 15 minutes after DMPO addition is shown in Figure 2A, which is similar to the ones from the aliquot taken at 5 and
9 minutes after DMPO addition (Figure S4). This similarity suggests that the radical species observed in EPR spectroscopy is the predominant species at the steady state during the electrolysis and not all of the transient ROS involved in the catalytic cycle may be captured in our experiments. Control experiments include the DMPO-added electrolysis without Rh\textsuperscript{III} pre-catalyst (Figure 2B), the mixture between DMPO and 0.5 mM KO\textsubscript{2} as a surrogate of O\textsubscript{2}•\textsuperscript{−} (Figure 2C and Figure S5), as well as the mixture between DMPO and 0.5 mM 2-hydroperoxypropan-2-ylbenzene (PhC(CH\textsubscript{3})\textsubscript{2}OOH, cumene hydroperoxide) as a surrogate of H\textsubscript{2}O\textsubscript{2}/•OH (Figure 2D and Figure S5). The captured ROS during electrolysis is predominantly O\textsubscript{2}•\textsuperscript{−}, based on the similar spectra shown in Figure 2A and 2C. The similarity between Figure 2A and 2B suggests that it is likely that the electrochemistry of Si nanowire other than Rh species is responsible for the generation of O\textsubscript{2}•\textsuperscript{−}.

Figure 2. Electron paramagnetic resonance (EPR) spectra depicting the adducts formed in the reaction of 50 mM DMPO (5,5-dimethyl-1-pyrroline N-oxide): (A) the electrolysis with Rh catalyst during CH\textsubscript{4}-to-CH\textsubscript{3}OH conversion; (B) control electrolysis in the absence of Rh catalyst; (C) 0.5 mM potassium superoxide (KO\textsubscript{2}); (D) 0.5 mM 2-hydroperoxypropan-2-ylbenzene (PhC(CH\textsubscript{3})\textsubscript{2}OOH, cumene hydroperoxide). Unless otherwise noted, in the electrolyte solution, 0.1 M tetrabutylammonium perchlorate (TBAClO\textsubscript{4}) in 1,2-difluorobenzene (1,2-DFB). Following previously reported condition,\textsuperscript{20} chronoamperometry was conducted at −1.4 V vs. SCE with Si nanowire working electrode under a constant flow of CH\textsubscript{4}/air mixture \(P_{\text{CH}_4}/P_{\text{air}} = 35\) in a customized electrochemical reactor (Figure S1) under ambient pressure.
We propose to quantify the generated ROS, predominantly $\text{O}_2^{*-}$ at steady-state, by colorimetric assay with the use of nitroblue tetrazolium (NBT) chloride as a $\text{O}_2^{*-}$-selective chromogen. NBT is reported to selectively react with the $\text{O}_2^{*-}$ over $\text{H}_2\text{O}_2$ and other ROS, leading to the emergence of a purple color in monoformazan, with a maximum absorption peak at $\sim530$ nm, from a pale yellow background. The stoichiometric reactivity between NBT and $\text{O}_2^{*-}$ (1:2), ensured by utilizing a concentration of $\text{NBT} / \text{O}_2^{*-} < 2$, enables the use of UV-Vis absorption spectroscopy for the quantification of $\text{O}_2^{*-}$ generation. Additionally, the NBT exhibits minimal reductive activity in organic solvent within its electrochemical window, which was not only reported in previous literature but also shown in our cyclic voltammograms (Figure S6) and chronoamperometry (Figure 3A) on a glassy carbon working electrode in 0.1 M TBAClO$_4$ solution.

**Figure 3.** Quantification of superoxide ($\text{O}_2^{*-}$) with $\text{O}_2^{*-}$-selective chromogen nitroblue tetrazolium (NBT). (A) Chronoamperometry with glassy carbon working electrode in Ar. (B) The absorbance at 600 nm in 1,2-DFB of a fixed concentration of KO$_2$, a surrogate of ephemeral $\text{O}_2^{*-}$, for varying concentrations of NBT. $\varepsilon_{600\text{nm}}$, the established absorption coefficient at 600 nm of the yielded monoformazan from stoichiometric reaction between NBT and $\text{O}_2^{*-}$: (C) and (D) The yield of ROS ($Y_{ROS}$), determined as the detected $\text{O}_2^{*-}$ normalized by average electric current, are displayed against electrolysis duration with Si nanowire array of 15 µm length as working electrode. (C) CH$_4$/air atmosphere ($P_{\text{CH}_4}/P_{\text{air}} = 35$) with (purple, $n = 4$) and without (orange, $n = 3$) 1 mM Rh$^{\text{III}}$. (D) N$_2$/air atmosphere ($P_{\text{N}_2}/P_{\text{air}} = 35$) with (yellow, $n = 5$) and without (blue, $n = 5$) 1 mM Rh$^{\text{III}}$. – 1.4 V vs. SCE in 1,2-DFB of 0.1M TBAClO$_4$. Error bars denote standard deviations.
of 1,2-DFB. Thus, when added during the electrolysis under \( \text{CH}_4 \)-to-\( \text{CH}_3\text{OH} \) condition, the NBT will have minimal interference with the \( \text{O}_2 \)-reducing electrode and act as a \( \text{O}_2^- \) scavenger for a colorimetric quantification of the accumulated \( \text{O}_2^- \). While multiple methods including fluorescence measurements are viable for the \( \text{O}_2^- \) quantification\(^{38}\), the absorbance at 600 nm from monoformazan after the reaction between NBT and \( \text{O}_2^- \) was chosen in order to mitigate interference from the optical absorbance and phosphorescence of Rh species (630–750 nm).\(^{40}\) Furthermore, due to the ephemeral nature of \( \text{O}_2^- \) that hinders the preparation a standard solution of known \( \text{O}_2^- \) concentration\(^ {35,41}\), we specifically designed experiments that establish a calibration curve of the absorbance at 600 nm which accounts for the stoichiometric reaction between NBT and \( \text{K}_2\text{O}_2 \), the \( \text{O}_2^- \) surrogate.\(^ {35}\) When an increasing concentration of NBT was mixed with a fixed concentration of \( \text{K}_2\text{O}_2 \) in 1,2-DFB, the absorbance at 600 nm follows a linear correlation before plateauing (Figure 3B), illustrating a stoichiometric reaction between NBT and \( \text{O}_2^- \) without other chromogenic side reactions. This led us to determine the absorption coefficient at 600 nm of the yielded monoformazan, \( \varepsilon_{600\text{nm}} = 4327 \text{ M}^{-1} \text{cm}^{-1} \) (\( \text{R}^2 = 0.97 \)) (Section 3B of the Supplementary Information). Similar linear response between NBT and \( \text{O}_2^- \) was also observed in the presence of Rh catalysts in 1,2-DFB (Figure S7), which suggests that the presence of Rh\( ^{\text{III}} \) in the bulk solution does not interfere with the colorimetric assay.

The rate of \( \text{O}_2^- \) generation was quantified with the use of NBT in the nanowire-based cascade system for \( \text{CH}_4 \)-to-\( \text{CH}_3\text{OH} \) conversion. Under the same electrochemical conditions with the use of Si nanowire array electrode of 15 \( \mu \text{m} \) length at \(-1.4 \text{ V} \) vs. SCE, aliquots of electrolyte solution were sequentially sampled, measured for optical absorbance at 600 nm, and applied to calculate the amount of accumulated \( \text{O}_2^- \) (Section 3C of the Supplementary Information). The yields of net accumulated \( \text{O}_2^- \) (\( Y_{\text{ROS}} \)), normalized by the average electric current during electrolysis, were shown as a function of electrolysis duration in \( \text{CH}_4/\text{air} \) and \( \text{N}_2/\text{air} \) atmosphere (\( P_{\text{CH}_4}/P_{\text{air}} \) and \( P_{\text{N}_2}/P_{\text{air}} = 35 \); Figure 3C and 3D, respectively). The initial slopes of the \( Y_{\text{ROS}} \) before plateauing (\( \partial Y_{\text{ROS}}/\partial t \)) were determined as the rate of electrochemical ROS generation in the compartmentalized cascade reaction. \( \partial Y_{\text{ROS}}/\partial t = 18\pm4 \) and \( 22\pm4 \) \( \text{\mu M} \cdot \text{mA}^{-1} \cdot \text{min}^{-1} \) in \( \text{CH}_4/\text{O}_2 \) atmosphere with the presence and absence of 1 mM Rh\( ^{\text{III}} \) (\( n = 4 \) and \( n = 3 \); purple and orange traces in Figure 3C, respectively); \( \partial Y_{\text{ROS}}/\partial t = 16\pm4 \) and \( 23\pm3 \) \( \text{\mu M} \cdot \text{mA}^{-1} \cdot \text{min}^{-1} \) in the \( \text{N}_2/\text{air} \) with the presence and absence of 1 mM Rh\( ^{\text{III}} \) (\( n = 5 \); yellow and blue traces in Figure 3D, respectively). The similar values of \( \partial Y_{\text{ROS}}/\partial t \) between \( \text{CH}_4 \) and \( \text{N}_2 \) atmosphere suggests that the ROS formation...
is independent of the gaseous environment. The similar values of $\frac{\partial Y_{\text{ROS}}}{\partial t}$ with and without Rh$^{\text{III}}$ suggests that the electrode surface of Si nanowire is primarily responsible for ROS generation, albeit the presence of Rh$^{\text{III}}$ does seem to lower the ROS yield. Here we note that $\frac{\partial Y_{\text{ROS}}}{\partial t}$ could be underestimated, because NBT is less reactive towards other ROS that may be concurrently generated during the electrochemical process.

**Experimental determination and analysis of reaction efficiency $\gamma$**

Our successful quantification of the electrochemical ROS generation rate ($\frac{\partial Y_{\text{ROS}}}{\partial t}$) led to an experimentally determined value of reaction efficiency $\gamma$. As the reductive current is responsible for the generation of both ROS and CH$_4$-activating Rh$^{\text{II}}$, the equation for $\gamma$ in Figure 1C can be written as:

$$\gamma = \frac{R_p}{R_s} \sim \frac{N_{\text{CH$_3$OH}}}{N_{\text{Rh(II)}}} = \frac{N_{\text{CH$_3$OH}}}{\int I dt - \int I F_{\text{Faradaic}} V \frac{\partial Y_{\text{ROS}}}{\partial t} dt}$$

(5)

Here $I$ denotes the electric current, $F_{\text{Faradaic}}$ the Faradaic constant, and $V$ the volume of electrochemical reactor. Equation (5) leads to $\gamma = 81\%$ for a 3-hr electrolysis of CH$_4$ activation (Section 1D of the Supplementary Information), based on the results of our previous report$^{20}$ and the value of $Y_{\text{ROS}}$ determined in Figure 3. The experimentally determined value of $\gamma$ is relatively close to unity, suggesting that a large portion of the generation Rh$^{\text{II}}$ activates CH$_4$ before diffusing out the nanowire array despite the high reactivity between Rh$^{\text{II}}$ and O$_2$ (Figure 1C).

In an effort to compare our experimentally determined $\gamma$ values with the theoretical maximum, we numerically calculated the values of $\gamma$ based on the established theoretical framework for a nanowire-based compartmentalization. Following the model displayed in Figure 1C, the calculated values of $R_s$ (Figure 4A and 4D), $R_p$ (Figure 4B and 4E), and the Rh$^{\text{II}}$ flux diffusing out of compartment $R_i$ (Figure 4C and 4F) were displayed as a function of $k_1$ and $F_V$ (Section 1B of the Supplementary Information). Those calculations use $k_e \to \infty$, $C_{\text{CH$_4$}} = 9.54$ mM$^{20}$, $C_{\text{Rh, total}} = 1$ mM, and $k_2 = 2.9 \times 10^4$ M$^{-2}\cdot$s$^{-1}$ for Rh$^{\text{II}}$-initiated CH$_4$ activation within nanowire array as determined in our previous report.$^{20}$ Because the rate of electrochemical reduction of Rh$^{\text{III}}$ ($k_1$) was not readily determinable in our system, $k_1$ was assigned as a range of values spanning four order of magnitude ($10^6$–$10^{10}$ s$^{-1}$) based on typical range reported for electron transfer of metalloporphyrin complexes in literature.$^{42}$ Nonetheless, Figure 4 shows that the effect of
compartmentalization is not sensitive to the value of $k_1$, evident as the $k_1$ term cancels out in Equations S14, S18, and S19 during the derivation as long as $k_1$ is sufficiently large ($\geq 10^6$ s$^{-1}$) (Section 1B in the Supplementary Information). However, the values of $R_s$, $R_p$, and $R_i$ are sensitive to the value of $F_V$, with an increased $F_V$ value leading to increase fluxes both outward and inward of the compartment. Because the value of $F_V$ is dependent on the nanowire array’s morphology, such a trend suggests that we can control and possibly optimize the mass transport across the compartment, by controlling the length $L$ of nanowire array based on equation (2).

Comparison between the experimental value of $\gamma$ with simulation results suggests that the Rh-based organometallic catalysis enabled by nanowire array is indeed functioning near its theoretical limit. Given the strong dependence on the value of $F_V$ for $R_s$, $R_p$, and $R_i$, we envisioned that $\gamma$ is mostly a function of $F_V$, whose relationship is displayed as the red trace in Figure 5. While $R_s$, $R_p$, and $R_i$ all increase with larger value of $F_V$ (vide supra), overall a larger $F_V$ value tends to

Figure 4. Graphical representations of substrate conversion ($R_s$), product formation ($R_p$), and intermediate outflux ($R_i$) in the compartmentalized system. Panels (A), (B), and (C) represent $R_s$, $R_p$, and $R_i$, respectively, as a function of both $F_V$ and $k_1$. Panels (D), (E), and (F) represent $R_s$, $R_p$, and $R_i$, respectively, as a function of $F_V$ for a constant value of $k_1$ (1.0 ×10$^6$ s$^{-1}$). $k_2$ was experimentally determined to be 2.9×10$^4$ M$^{-2}$·s$^{-1}$ within the nanowire array in our previous report.$^{20}$
decrease the value of $\gamma$ (Figure 5). Such a trend is corroborated with our previous observation that nanowire array of longer length $L$, hence smaller $F_V$ value based on equation (2), corresponds to a larger yield of CH$_3$OH before mass transport becomes rate-limiting.$^{20}$ In comparison, the value of $\gamma$ for a non-compartmentalized scenario, *i.e.* homogenous solution without nanostructured electrode, is also shown as the black trace in Figure 5 (Section 1C in the Supplementary Information). A clear difference is observable as the value of $\gamma$ for non-compartmentalized scenario is virtually near zero (at most 0.001% indeed). We also positioned our experimentally determined $\gamma$ value in Figure 5, after we determined $F_V = 20$ s$^{-1}$ given $L = 15$ µm and $D = 5.62 \times 10^{-10}$ m$^2$s$^{-1}$ in 1,2-DFB as measured before.$^{20}$ The error bar in Figure 5 represents the approximation incurred when deriving the expression for $F_V$ (Equation 2) (Section 1A in the Supplementary Information). A good agreement between the experimental and theoretical values of $\gamma$ for nanocompartment was observed (Figure 5), yet the slightly higher value of experimentally derived $\gamma$ might originate from the underestimation of $\partial Y_{ROS}/\partial t$ (vide supra). The agreement indicates that minimal unforeseen side reactions, if any, are present in the catalyst system and the

![Figure 5](image.png)

*Figure 5.* Reaction efficiency $\gamma$ plotted as a function of diffusive conductance $F_V$ for the scenarios with nanowire-enabled compartmentalization (red trace) and $\gamma$ plotted as a function of $k_1$ without nanowire-enabled compartmentalization (black trace). The experimentally determined data point of $\gamma$ for nanowire array of 15 µm length is represented by the star. The error bar presents the approximation when deriving the experimental value of $F_V$ (Section 1A in the Supplementary Information).
A proposed benefit of a nanowire-generated O$_2$-free microenvironment for Rh$^{III}$-initiated CH$_4$ activation is well demonstrated.

Despite the findings that O$_2$$^-$ is the dominant ROS at steady state, we propose that O$_2$$^-$ is not the immediate oxidant that reacts with Rh$^{III}$—CH$_3$ for CH$_3$OH formation. We found that under strictly dry conditions, no CH$_3$OH was observed in a mixture of KO$_2$ and as-synthesized Rh$^{III}$—CH$_3$. Yet a stoichiometric amount of CH$_3$OH, calculated by Rh$^{III}$—CH$_3$, was observed in experiments with KO$_2$ “wet” in 1,2-DFB (5.1±0.3 mM H$_2$O based on Karl Fischer titration), as well as with cumene hydroperoxide or t-Butyl hydroperoxide in dry 1,2-DFB (Sections 4 of the Supplementary Information).\textsuperscript{20} Such observations prompted us to propose that trace H$_2$O$_2$ constantly generated during the electrolysis is the immediate reactant towards Rh$^{III}$—CH$_3$. We speculate that the electrochemical reduction of O$_2$ to O$_2$$^-$ is followed by a chemical protonation step to generate other ROS such as a hydroperoxyl radical (HO$_2$)$^\bullet$,\textsuperscript{43} which is susceptible to heterolytic and homolytic cleavages and eventually converges on H$_2$O$_2$.$^\text{44-46}$ Whether the conversion of HO$_2$$^\bullet$ to H$_2$O$_2$ proceeds electrochemically or chemically should be dependent on the proton donor concentration in solution and the reduction potential applied.$^\text{46}$ Once the hydroperoxide species is formed, CH$_3$OH formation proceeds from its reaction with Rh$^{III}$—CH$_3$. Such mechanistic consideration would be useful in designing other ROS-initiated CH$_4$-activation reactions.

Additional design insights are available from our results. We examined the dependence of $\gamma$ under different hypothetical values of CH$_4$-activation rate constant $k_2$. Smaller values of $k_2$ significantly lowers $\gamma$, \textit{i.e.} the efficiency of compartmentalization created by nanowire array (Figure S8). Such a trend is reasonable since a lower value of $k_2$ will lead to more prominent outward flux $R_i$ of the unreacted Rh$^{II}$ species which will introduce a larger percentage of undesirable Rh$^{II}$ deactivation. Therefore, while our Rh-based catalysis demonstrates the benefits of compartmentalization by constructing a catalytic cycle of seemingly incompatible steps for organometallics, we caution that the efficacy of this strategy depends on the specific chemical system under consideration. As the value of $\gamma$ depends on $F\nu$ and thus the nanostructure’s morphology, such as nanowire length $L$ in our case, there exists an optimal morphology of nanostructures for specific organometallic compounds’ reactivities in order to create an effective microenvironment and efficient cascade reactions with minimal detrimental deactivation. A
quantitative evaluation of reaction efficiency $\gamma$, however estimated, is recommended in order to justify the introduction of nanostructures and micro-environment. A general numerical design framework of nanostructures for a typical organometallic catalytic cycle that includes oxidative addition and reductive elimination is currently being developed in the authors’ laboratory.

CONCLUSION

In this work, we applied the concept of reaction efficiency $\gamma$ in biochemical cascades to quantitatively evaluate the efficacy of compartmentalization for organometallic reactions with the use of nanowire array electrodes. High $\gamma$ value approaching unity, the theoretical limit, was experimentally observed, suggesting minimal detrimental side reactions. This observation indicates that with proper design it is possible to employ nanomaterials to spatially control organometallic reactions and achieve efficient cascade with ephemeral intermediates, analogous to the biological counterparts with near-unity $\gamma$ values. This work quantitatively highlights the transformative power of spatial control at nanoscale for new chemical reactivity.
ASSOCIATE CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI:
   Full experimental details, synthetic procedures, electrochemical characterizations, mathematical derivations, and additional figures.

Author Information
C. L. supervised the project. C. L. and B. S. N. designed experiments and wrote the paper. B. S. N. synthesized the compounds and conducted electrochemical characterizations with assistance from D. M. D.. B. J. J. performed the mathematical derivations on the compartmentalized system. All the authors discussed the results and assisted during the manuscript preparation.

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Notes
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How to quantify the efficacy of microscopic compartmentalization?

Nanowire array → Bulk solution
Rh^{III} → e^- → Rh^{II} → CH_3 → ROS → CH_3OH

CH_4 → CH_3OH
deadcat, e-chem nanowire R.T., air
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