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# An Organometallic Dismutase – Self-sufficient Formaldehyde-to-Methanol Conversion

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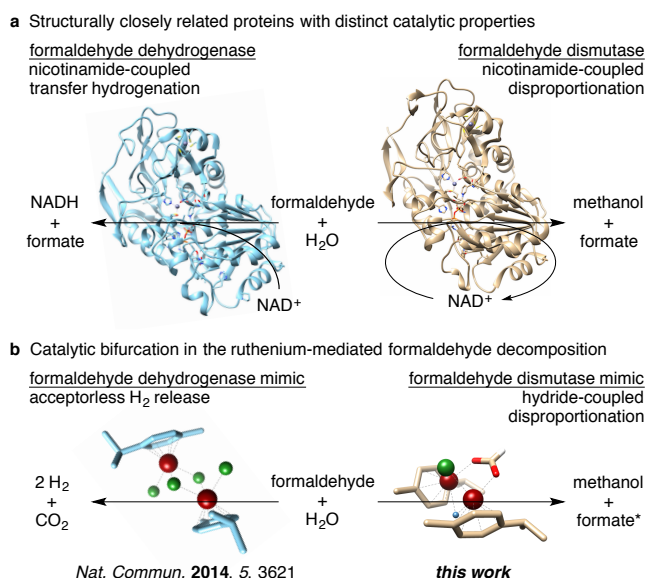
**Abstract:** The catalytic networks of methylotrophic organisms featuring redox enzymes for the activation of one-carbon moieties can serve as great inspiration in the development of novel homogeneously catalysed pathways for the interconversion of C<sub>1</sub> molecules at ambient conditions. An imidazolium-tagged arene-ruthenium complex was identified as an effective functional mimic of bacterial formaldehyde dismutase that provides a novel and highly selective route for the conversion of formaldehyde to methanol in absence of any external reducing agents. Moreover, secondary amines are reductively methylated by the organometallic dismutase mimic in a redox self-sufficient manner with formaldehyde acting both as carbon source and reducing agent.

## Introduction

Methanol and formaldehyde are key platform chemicals which are formed industrially from syngas on a megaton scale.<sup>[1–3]</sup> Currently, these reactions are carried out at high temperatures and pressures over various different heterogeneous catalysts.<sup>[4,5]</sup> Milder reaction conditions for the conversion of one-carbon entities have been achieved using well-defined molecular metal catalysts. Here, the most recent successful examples commonly focussed on highly oxidized starting materials, that is, carbon dioxide and formic acid. In addition to the well-developed CO<sub>2</sub>-to-formate reduction protocols,<sup>[6–11]</sup> in the past five years both multi-metallic approaches<sup>[12]</sup> and single-site catalyst systems<sup>[13–17]</sup> have emerged en route to homogeneously catalysed methanol synthesis from CO<sub>2</sub>. Moreover, methanol production was attempted by catalytic disproportionation of formic acid. Fighting against the favourable formate decomposition,<sup>[18]</sup> in 2014 a ruthenium-triphos complex was reported to generate MeOH in up to 50% yield, along with at least two equivalents of CO<sub>2</sub>.<sup>[19]</sup>

In Nature, formaldehyde plays a much more pronounced role within the family of C<sub>1</sub> molecules. Based on an evolutionarily conserved detoxification mechanism, various methanol-tolerant or even methanol-feeding microorganisms have developed a biocatalytic machinery to deal with, and benefit from formalin. In addition to the capability to include formaldehyde into the biosynthetic carbon fixation via the ribulose monophosphate pathway,<sup>[20,21]</sup> methylotrophs exploit formalin, rather than methanol, as source of reduction equivalents. Here, preactivation of CH<sub>2</sub>O by formation of hemithioacetal conjugates with either cofactors (mycothiol or glutathione)<sup>[22,23]</sup> or protein-bound mercaptanes<sup>[24]</sup> allows for a transfer hydrogenation to NAD<sup>+</sup>, where NADH is liberated to serve as biological reductant (Scheme 1, top left). Inspired by this mode of action, we recently reported on a biomimetic ruthenium-based H<sub>2</sub>-release system using methanediol as simple tetrahedral formaldehyde conjugate analogue and hydrogen as abiotic NADH equivalent (Scheme 1, bottom left).<sup>[25]</sup>

A number of C<sub>1</sub>-feeding bacterial strains of e.g. *Pseudomonas putida*, *Staphylococcus aureus* or *Mycobacterium gastri* supplement their formaldehyde metabolism with a second pathway using dismutases, independent of external sacrificial redox partners (Scheme 1, top right).<sup>[26–28]</sup> On one side, these



**Scheme 1.** **a**, The primary routes of the biological formaldehyde metabolism proceed via dehydrogenation and disproportionation by two structurally linked, nicotinamide-depending oxidoreductases. **b**, Bioinspired ruthenium-catalysed H<sub>2</sub>-release and methanol synthesis from hydrated formaldehyde. \* Formate serves as second reduction equivalent for the conversion of formaldehyde to methanol under liberation of CO<sub>2</sub>.

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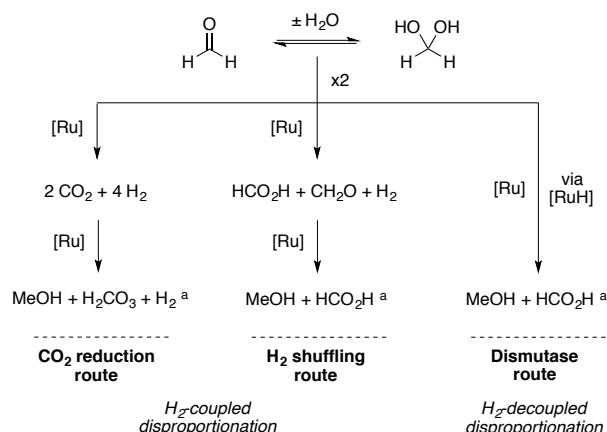
formalin disproportionating enzymes exhibit a considerable structural and functional resemblance to the glutathione-independent zinc-containing dehydrogenases, with a sequence similarity greater 70% (Supplementary Fig. 1).<sup>[29]</sup> As a result of a firmly immobilized nicotinamide-dinucleotide cofactor inside the active site,<sup>[30,31]</sup> however, initial dehydrogenation of conjugated formalin is accompanied by reduction of a second formaldehyde moiety. Hence the deviated catalytic behaviour provides both methanol and formate from two molecules of formaldehyde and water. Considering the analogy of NADH as biological hydrogen carrier, and our lately described bioinspired process featuring acceptorless H<sub>2</sub> liberation,<sup>[25]</sup> we envisioned that modification of the organometallic species and/or the reaction environment of our original protocol will lead to a novel homogeneously catalyzed formaldehyde-to-methanol converting system, (Scheme 1, bottom right) yet unprecedented in the context of abiotic C<sub>1</sub>-valorization pathways.<sup>[32,33]</sup>

Recently, we reported on the possibility to incorporate the ruthenium-based formaldehyde dehydrogenase mimic into an artificial metabolism to work in concert with methanol-activating enzymes, providing a room temperature pathway for the MeOH-to-H<sub>2</sub> conversion and showcasing the potential of chemoenzymatics in small molecule activation.<sup>[34]</sup> However, in our crimp-top setup for the in situ gas phase analysis, apparent turnover numbers of H<sub>2</sub> liberation in an aqueous phosphate buffer lacked behind the uncoupled system, which can in parts be attributed to unfavourable metal-protein interactions, but which on the other hand might be related to reversibility of the process via formalin reduction under elevated H<sub>2</sub> pressure. This finding would now serve as starting point for the redirection of the catalytic profile towards a formaldehyde dismutase mimic that is disclosed in this communication.

## Results and Discussion

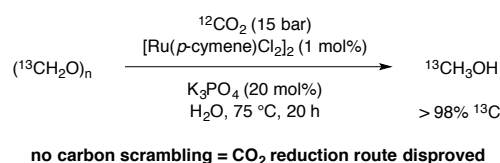
To our delight, already slight modifications of our parent [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>-catalysed H<sub>2</sub> release protocol, namely a closed vessel system and increased reaction temperatures, resulted in a functional dismutase mechanism and further optimization with regard to the nature and stoichiometry of the additives led to an efficient catalytic disproportionation (Supplementary Table 1-3). While initial attempts provided methanol from paraformaldehyde in a 1:1 stoichiometry, formalin decomposition with 1 mol% of [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> at 80 °C in phosphate buffer (0.4 m, pH 6) proceeded with increased yields of MeOH (75%) as a result of formate dehydrogenation to allow for the reduction of a second formaldehyde equivalent.<sup>[35]</sup> For the primary disproportionation, various mechanisms can be assumed (Scheme 2). Hence, studies aiming to elucidate the actual catalytic pathway have been conducted.

Hydrolysis of paraformaldehyde would in any of our proposals lead to free formaldehyde in equilibrium with its hydrated form methanediol. Initial investigations of the pH-dependency of the reaction quickly revealed that the ruthenium-independent Cannizzaro-type disproportionation appears only as background reaction at pH >9.5 (Supplementary Table 4) and, thus, cannot be considered a productive pathway. Under the



**Scheme 2.** Proposed routes for the catalytic formaldehyde disproportionation based on H<sub>2</sub>-coupled dehydrogenation/hydrogenation pathways or the dismutase-like catalysis via intermediary hydride species. <sup>a</sup> H<sub>2</sub>/HCO<sub>2</sub>H can potentially act as reducing agents for another equivalent of formaldehyde.

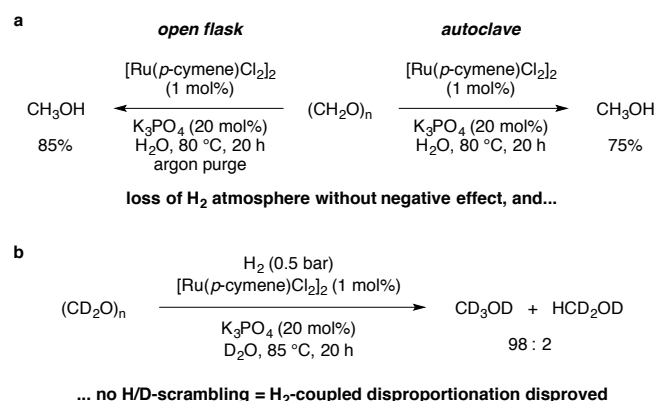
assumption of free H<sub>2</sub> being involved as redox mediator, two hydrogen-coupled routes are feasible. As methanediol has been shown to readily dehydrogenate to yield CO<sub>2</sub> and H<sub>2</sub> it was considered that in a closed system the direct reduction of CO<sub>2</sub> to methanol might be occurring (Scheme 2, left). However, neither precharging of the reaction vessel with carbon dioxide nor the removal of superfluous CO<sub>2</sub> by Ca(OH)<sub>2</sub> resulted in measurable effects on the methanol yields (Supplementary Table 5). This suggests that direct CO<sub>2</sub> reduction might not be the primary mechanism for methanol formation. Additionally, dismutation of <sup>13</sup>C-labelled paraformaldehyde was conducted under elevated pressure of <sup>12</sup>CO<sub>2</sub> to get further inside into the potential role of carbon dioxide. While yields were not affected by the level of CO<sub>2</sub> in the pressurized atmosphere (Supplementary Table 6), analysis of the methanol obtained from <sup>13</sup>CH<sub>2</sub>O-disproportionation under 15 bar of <sup>12</sup>CO<sub>2</sub> by proton NMR provided no significant sign of <sup>12</sup>CH<sub>3</sub>OH (Supplementary Fig. 2), suggesting that carbon dioxide was not incorporated from the overlaying atmosphere via a CO<sub>2</sub> reduction pathway (Scheme 3).



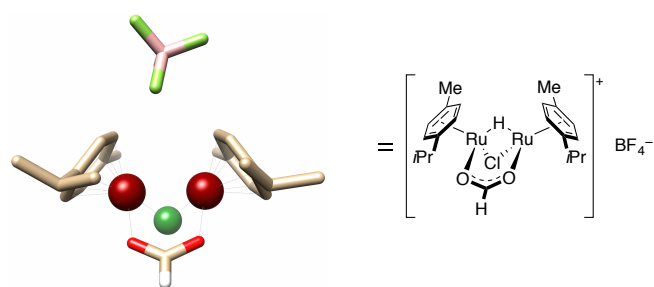
**Scheme 3.** <sup>13</sup>C-Labeling experiment to exclude the possibility of carbon dioxide as formal disproportionation intermediate.

In an alternative route, methanol formation could result from the direct reduction of formaldehyde either by another hydrogen-coupled process exploiting free H<sub>2</sub> as redox mediator (Scheme 2, centre), or by the dismutase-like dehydrogenative generation of reducing ruthenium hydride species from the tetrahedral formalin (Scheme 2, right). Examination of the

reaction's gas phase by pressure monitoring and headspace GC-TCD analysis gave clear evidence for the formation of hydrogen gas in the initial period of the process. All the more surprising, we found that formalin disproportionation was also taking place in an open flask setup rather than in an autoclave, and even under constant removal of the gas phase by argon purging, strikingly high yields of methanol were achieved (Scheme 4a). Further confirmation of an H<sub>2</sub>-decoupled pathway was obtained from the results of the ruthenium-catalyzed dismutation of deuterated formaldehyde under H<sub>2</sub> pressure. Here, less than 2% of partially H-containing methanol were detected, which reflects exactly the isotopologic composition of the commercial (CD<sub>2</sub>O)<sub>n</sub> used as starting material in this experiment (Supplementary Fig. 3). The complete absence of H/D scrambling through the mixed H<sub>2</sub>/D<sub>2</sub> atmosphere can serve as strong endorsement for the disproval of any gaseous redox mediators (Scheme 4b). Hence, the ruthenium-catalysed formalin disproportionation is most likely to proceed via a truly dismutase-like mechanism with a catalyst-bound hydride mimicking the intimate enzyme-nicotinamide arrangement. A catalytically potent dimeric hydride complex has been isolated and characterized (Figure 1).

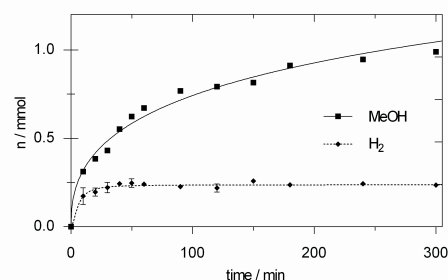


**Scheme 4.** Gas phase removal and deuterium labelling experiments to elucidate the role of H<sub>2</sub> gas as potential redox mediator



**Figure 1.** Crystallization of in situ formed formiato-bridged ruthenium dimers was achieved by precipitation as tetrafluoroborate salt. Crystal structure analysis shows a symmetric arrangement of the cymene donors and both formate and chloride as bridging ligands. Although X-ray diffraction could not help to allocate the hydridic hydrogen between the two ruthenium centres, clear evidence for the hydride nature of the complex was obtained by spectroscopic and spectrometric methods.<sup>[25]</sup> For detailed crystallographic data (CCDC 1471617), see appendix.

At first glance, these findings somewhat contradicted our previous report on the acceptorless H<sub>2</sub> production from formalin employing a very similar catalyst system. However, close inspection of all parameters exposed the hidden key for this catalytic bifurcation. As introduced during our attempt to exploit the ruthenium-based dehydrogenase mimic in a chemoenzymatic approach,<sup>[34]</sup> the phosphate-containing reaction medium proved to have a major influence on the behavior of the dimeric ruthenium catalyst. As opposed to the formalin dehydrogenation by [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> in absence (or at low concentrations) of phosphate that led to a strong and constant rise in pressure, already 20 mol% of K<sub>3</sub>PO<sub>4</sub> substantially reduced the initial hydrogen formation which quickly came to a complete rest at approximately 5% conversion (Supplementary Fig. 4+5). In situ analysis of the optimized dismutation process by NMR and headspace GC-TCD also revealed the rapid build-up of methanol, formate and H<sub>2</sub> during the first minutes. However, only the methanol production continued steadily over hours, explaining the good selectivity observed in the formalin decomposition (Figure 2).



**Figure 2.** Constant methanol formation vs. discontinuous H<sub>2</sub> release.

While the underlying role of the phosphate additive still remains unclear and its elucidation will require a much deeper investigation, we expected that further fine-tuning of the reaction conditions would already now allow us to provide a highly efficient formaldehyde-to-methanol protocol. To determine also the effect that modifications to the ruthenium precatalyst impart upon the methanol yield of the reaction (Supplementary table 7), a range of complexes analogous to the commercial [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> were synthesized employing a recently developed microwave-assisted protocol.<sup>[36]</sup> In the dismutation, variation of the anionic counterion by different (pseudo)halides showed no influence of reaction rates or the yield of methanol after 20 h (Table 1, entries 1–4), which is in good agreement with the previously described exchange of bridging ligands during methanediol dehydrogenation.<sup>[24]</sup> In contrast, the substitution pattern and particularly the polarity of the arene ligand proved to be decisive for the activity of the methanol-generating process. While more hydrophobic η<sup>6</sup>-donors led to decreased final concentrations of the alcohol (Table 1, entry 6), decoration of the arene by polar hydroxy groups to facilitate aqueous solubility resulted in slightly improved catalytic systems (Table 1, entries 7 & 8). By incorporation of a cationic 1,2-dimethylimidazolium unit,<sup>[37]</sup> a highly active ruthenium precatalyst was obtained that

showed excellent performance in the formalin dismutation with a final methanol yield of 93% (Table 1, entry 9), along with deteriorated dehydrogenation properties (Supplementary Fig 6). More importantly, the imidazolium-tagged dimer still exhibited good activity at considerably lower temperatures and reasonable conversions were achieved even at room temperature (Table 1, entry 10). For this most reactive dismutase mimic, turnover frequencies up to 1060 h<sup>-1</sup> were recorded and significant methanol formation was detected at ruthenium-loadings as low as 250 ppm (Supplementary table 8).

**Table 1.** Testing of ruthenium complexes for the self-sufficient methanol synthesis from paraformaldehyde.<sup>[a]</sup>

$3 (\text{CH}_2\text{O})_n + n \text{H}_2\text{O} \xrightarrow[\text{H}_2\text{O, T, 20 h}]{[\text{Ru}(\text{arene})\text{X}_2]_2 (1 \text{ mol\%}), \text{K}_3\text{PO}_4 (20 \text{ mol\%})} 2n \text{CH}_3\text{OH} + n \text{CO}_2$				
Entry	arene	X	T [°C]	MeOH <sup>[b]</sup>
1	<i>p</i> -cymene	Cl	80	75 %
2	<i>p</i> -cymene	Br	80	68 %
3	<i>p</i> -cymene	I	80	66 %
4	<i>p</i> -cymene	SCN	80	68 %
5	toluene	Cl	80	70 %
6	hexamethylbenzene	Cl	80	50 %
7	2-phenylethanol	Cl	80	73 %
8	2-phenoxyethanol	Cl	80	79 %
9		Cl	80	93 %
10		Cl	25	58 %

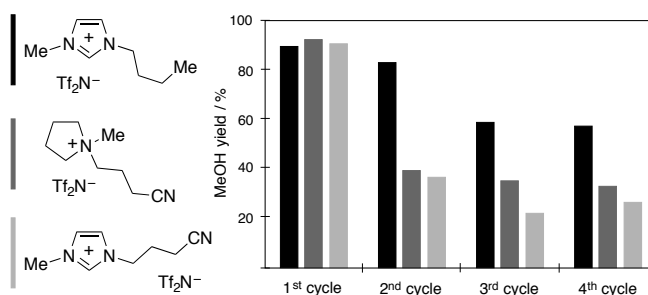
[a] Reactions run on a 2 mmol scale in 1 mL aqueous phosphate buffer (0.4 m, pH 6). [b] Conversions were determined by <sup>1</sup>H-NMR relative to 1,4-dioxane as internal standard. All values are normalized, taking into account the reaction stoichiometry allowing for a maximum of 67% methanol.

Currently, there is significant focus on environmentally benign methods for chemical procedures and in particular on the use of recyclable catalysts. Initial recharge experiments employing the commercial cymene ruthenium dimer already revealed a stable catalytic system with considerable activity over at least two successive formaldehyde recharges (Table 2). subsequent cycles, hence replacing the aqueous phase by an untreated formalin/phosphate solution, was noted for [bmim]NTf<sub>2</sub> as co-phase that exhibited a substantially higher long-term stability of the catalyst than the other ionic liquids tested so far (Figure 3). Nonetheless, there remains a need for further investigations on the ionic liquid-based recycling systems and in-depth studies in order to identify an optimal methodology are currently ongoing.

**Table 2.** Recharge experiments.<sup>[a]</sup>

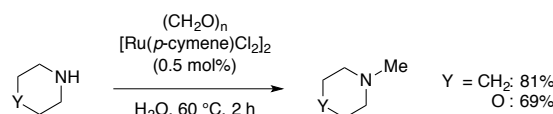
$(\text{CH}_2\text{O})_n \xrightarrow[\text{H}_2\text{O, 70 °C, 20 h}]{[\text{Ru}(\textit{p}\text{-cymene})\text{Cl}_2]_2 (0.1 - 1 \text{ mol\%}), \text{K}_3\text{PO}_4 (20 \text{ mol\%})} \text{CH}_3\text{OH}$				
Entry	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub>	cycle	MeOH	total TON
1	1 mol%	#1	75%	50
2		#2	75%	100
3		#3	30%	120
4	0.1 mol%	#1	59%	393
5		#2	12%	473
6		#3	3%	493

[a] Reactions run on 4 mmol scale in 2 mL of water in a sealed autoclave. Final concentrations of methanol were determined by <sup>1</sup>H NMR relative to 1,4-dioxane as internal standard. After each cycle, all volatiles were removed in vacuo, and paraformaldehyde, water and dioxane were replaced.



**Figure 3.** Recycling of the imidazolium-tagged arene ruthenium dimer using non-water-miscible ionic liquids as additive for biphasic formaldehyde-to-methanol conversion..

Based on the proposal that methanol formation occurred through reduction of free formaldehyde, the possibility of in situ formation and hydrogenation of even more reactive methylene compounds via condensation with the aldehyde appeared as a valuable synthetic extension of the disproportionation protocol. Initial attempts focused on secondary amines as additional reaction partners in order to study the redox self-sufficient reductive amination employing formaldehyde both as carbon source and reducing agent.<sup>[38]</sup> To our delight, methylation of cyclic secondary amines proceeded smoothly in presence of 0.5 mol% of the dimeric cymene ruthenium chloride with excellent yields of *N*-methylpiperidine and *N*-methylmorpholine of 81% and 69%, respectively, after only 2 h (Scheme 5). Opening up an entirely new perspective on the formalin redox chemistry, future investigations will cover the synthetic aspects of the formaldehyde decomposition in much greater details.



**Scheme 5.** Redox self-sufficient reductive *N*-methylation.

## Conclusions

In conclusion, we herein described a novel, homogeneously catalysed, selective formaldehyde-to-methanol transformation as a missing piece in the C<sub>1</sub>-interconversion puzzle. Inspired by the bacterial formaldehyde dismutase biocatalysts, using ruthenium arene complexes as activating species, it was shown that the reaction proceeds via formaldehyde reduction by metal-bound hydrogen species as redox cofactor analogues rather than through CO<sub>2</sub> hydrogenation, formate decomposition or Cannizzaro disproportionation. An imidazolium-tagged ruthenium complex did not only exhibit optimal catalytic properties but further allowed for the construction of biphasic reaction setups making use of ionic liquids for an easy catalyst recycling. In addition, the metal-mediated formalin decomposition could be employed in a synthetic manner where formaldehyde acts as sole stoichiometric reagent in a redox self-sufficient reductive methylation of secondary amines.

## Experimental Section

### General remarks

All chemicals were used as received without further purification, primarily from Sigma Aldrich or Strem Chemicals. Paraformaldehyde was purchased from Acros Organics (>95% Extra Pure), HPLC grade water used as the solvent was not degassed prior to use. (<sup>13</sup>CH<sub>2</sub>O)<sub>n</sub> were obtained from *Cambridge Isotope Laboratories* and (CD<sub>2</sub>O)<sub>n</sub> from *Sigma Aldrich*. <sup>1</sup>H- & <sup>13</sup>C-NMR spectra were recorded in CDCl<sub>3</sub> or D<sub>2</sub>O (≥99.5% deuterated, purchased from Fluorochem) on a Bruker Avance 300 (300 MHz). All chemical shifts (δ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) (δH = 0.00 ppm) unless otherwise stated. Selectivities for methanol are given as a percentage relative to the maximum two thirds conversion from paraformaldehyde referred to an internal standard and are the average of at least two runs unless otherwise mentioned. Headspace gas chromatography equipped with a TCD was carried out on a *Thermo Fischer Scientific GC-TCD*.

### General procedure for the ruthenium-catalyzed formaldehyde dismutation

To a 20 mL glass screw capped reaction vial furnished with a stirrer bar, [Ru(1-phenethyl-2,3-dimethylimidazolium)Cl<sub>3</sub>]<sub>2</sub> (16 mg, 0.02 mmol) and paraformaldehyde (pFA) (60 mg, 2.0 mmol) were added. K<sub>3</sub>PO<sub>4</sub> (8 mg, 0.4 mmol) and 1,4-dioxane standard were added followed by 2 mL of HPLC grade water, the reaction vial was sealed and heated at the desired temperature for the duration of the reaction with stirring. Upon completion, the reaction was cooled, shaken to ensure homogeneity and an aliquot was taken directly for NMR analysis after dilution with D<sub>2</sub>O.

### General procedure for the ruthenium-catalyzed N-methylation

Paraformaldehyde (300 mg, 10 mmol) and [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (6.1 mg, 0.01 mmol) were placed in a screw-neck vial, followed by the addition of water (1 mL) and the secondary amine (piperidine, 170 mg, 2.0 mmol; or morpholine, 174 mg, 2.0 mmol). The vial was closed, then placed in a pre-heated aluminium block at 60 °C and stirred for 2 h. After this time, the vial was cooled to room temperature, aqueous NaOH (2 M, 2 mL) was added, and the aqueous phase was washed with DCM (3 x 10 mL). The combined organic fractions were dried over MgSO<sub>4</sub> and Al<sub>2</sub>O<sub>3</sub> and the solvent was removed in vacuo to yield the desired amine (*N*-

methylpiperidine, 160 mg, 1.62 mmol, 81%; or *N*-methylmorpholine, 140 mg, 1.38 mmol, 69%).

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**Keywords:** bioinspired catalysis • ruthenium • methanol • ionic liquids • reductive amination

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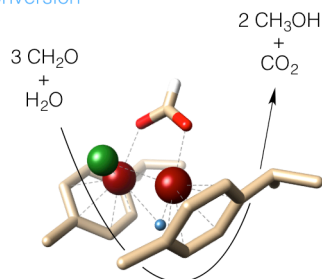
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Dimeric arene ruthenium complexes act as efficient organometallic functional mimics of bacterial formaldehyde dismutase, allowing for the production of methanol from paraformaldehyde in absence of any external reducing agents. In addition, the ruthenium-catalysed formaldehyde decomposition can be employed in a redox self-sufficient reductive methylation of secondary amines.

Bioinspired  
Formaldehyde-to-Methanol  
Conversion



*Dominic van der Waals, Leo E. Heim, Simona Vallazza, Christian Gedig, Jan Deska and Martin H. G. Prechtl\**

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**An Organometallic Dismutase – Self-sufficient Formaldehyde-to-Methanol Conversion**

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