Utilization of Formic Acid as C1 Building Block for the Ruthenium-Catalyzed Synthesis of Formaldehyde Surrogates

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Dialkoxymethanes are becoming increasingly important as fuel additives, formaldehyde surrogates, and chemical intermediates, but the effective synthesis remains challenging. Herein, the catalytic synthesis of dialkoxymethane products using a molecular catalyst is reported. The catalytic system, comprising the [Ru(triphos)(tmm)] in combination with the Lewis acid Al(OTf)₃, enables the direct synthesis of dialkoxymethane products with formic acid as C1 building block in high to excellent turnover numbers.

On the translation from a fossil based chemical industry to manufacturing with renewable carbon sources, the use of carbon dioxide (CO₂) as C1 building block is becoming increasingly important. However, the synthetic utilization of the unreactive starting material is highly challenging and requires tailored catalyst systems and strong reducing agents. This approach then enables the stepwise reduction of CO₂ to formic acid, formaldehyde or methanol derivatives with decreased oxidation states.[1] As transformations with CO₂ require complex engineering solutions, formic acid is often considered as preferred alternative for the CO₂-based synthesis of value-added chemicals.[2] The annual production of formic acid is currently attributed to 700 000 tons, mainly produced from the indirect carbonylation of methanol via methyl formate intermediate.[3] However, the pioneering work of Inoue et al. in 1976 paved the way for the catalytic hydrogenation of CO₂ to formic acid or methyl formate and the development of effective catalyst systems and hydrogenation processes.[4]

On the other hand, dialkoxymethanes are becoming increasingly important as fuel additives, formaldehyde surrogates and chemical intermediates.[5] For example, dimethoxy methane (DMM) and diethoxy methane (DEM) could be recently introduced as fuel additive, strongly reducing soot formation during the combustion in standard diesel engines.[6,7] The established production process for DMM is based on a two-step process, comprising the oxidation of methanol to formaldehyde over heterogeneous catalysts, followed by the condensation of formaldehyde with methanol (Scheme 1, A).[8] In this reaction the precious hydrogen equivalent, formed during the oxidation of methanol to formaldehyde, is unfortunately lost as water. Recently, a direct reductive approach starting from CO₂ could be introduced, enhancing the energy efficiency of the transformation and reducing the reaction steps. In detail, one molecular ruthenium catalyst allowed the sequential reduction and acetalization transformation.[8] Subsequent optimization studies using the established catalyst lead structure allowed reactions with increased TONs.[9] Additionally, a non-precious and efficient cobalt-triphos system could be established for this hydrogenation sequence of CO₂ to DMM.[10] Moreover, new catalyst concepts and reaction pathways enlarged the synthetic portfolio and paved the way to unprecedented DMM synthesis approaches.[6a,11]

In the next development step, the utilization of formic acid as readily available and more reactive alternative to CO₂ in the cascade reaction is envisaged, enabling to streamline the formation of DMM. Herein, the first catalytic utilization of formic acid as a C1 building block for the synthesis of selected dialkoxymethane products could be developed, facilitated by a molecular ruthenium complex and allowing to produce selected formaldehyde surrogates (Scheme 1, B).

In previous work, an active molecular ruthenium catalyst, cooperating with Lewis acids towards flexible cascade transformations could be established.[8a,b] The versatile triphos-based ruthenium catalyst [Ru(triphos)(tmm)] (triphos = 1,1,1-tris-...
(diphenylphosphinomethyl)ethane, \textit{tmm} = trimethylene methane) represents a robust hydrogenation catalyst, operating via a series of hydride transfer/protonolysis steps and allowing to activate CO\textsubscript{2} and challenging organic functionalities.\textsuperscript{[5]} Accordingly, the present investigation with formic acid was initiated with this [Ru(triphos)(tmm)] catalyst and aluminum tris(trifluoromethanesulfonate) Al(OTf)\textsubscript{3} as Lewis acidic co-catalyst. The Al(OTf)\textsubscript{3} acid was selected for this work as it showed the best results of previous reported work on DMM synthesis from CO\textsubscript{2}\textsuperscript{[6–9]} Generally, first reactions were carried out using molecular hydrogen at a pressure of 80 bar and 80 °C. As the acid-catalyzed condensation reaction of formic acid and methanol to methyl formate (MF) is expected to be the first step in the DMM cascade synthesis, the effect of Al(OTf)\textsubscript{3} concentrations on DMM yield was examined. Using the [Ru(triphos)(tmm)] catalyst in absence of acid did not result in formation of any detectable DMM product and only traces of MF were observed (Table 1, entry 1). This result corroborates, that formic acid cannot act as co-catalyst in this cascade reaction. However, using the ruthenium precursor in combination with Al(OTf)\textsubscript{3} in varying concentrations resulted in the formation of DMM as main reaction product. In detail, when Al(OTf)\textsubscript{3} acid was used in 6.0 or 12.5 μmol (2 and 4 eq.), astonishing TONs of 796 and 790 were obtained (Table 1, entries 2–3) when compared to the reaction in absence of the co-catalyst (Table 1, entry 1). The yield and TON of DMM were increased to 44% and 849, when an optimal load of 25 μmol of Al(OTf)\textsubscript{3} was used (Table 1, entry 4). However, no increase in TON was observed when additional equivalents Al(OTf)\textsubscript{3} were employed (Table 1, entries 5 and 6).

In the subsequent development step, the effect of different initial concentrations of formic acid on DMM formation was evaluated (Table 2 and Figure 1). Employing the optimal Al(OTf)\textsubscript{3} loading from the previous screening, the concentration of formic acid was varied in the range of 0.8–4.9 mmol/mL (Table 2). Using formic acid in 0.8 mmol/mL concentration resulted in the formation of DMM in 51% yield (TON = 292) with 94% selectivity (Table 2, entry 1). Increasing the concentration of formic acid to 2.1 and 2.9 mmol/mL afforded the DMM product in 45–47% yield (Table 2, entries 2 and 3). Accordingly, the increase of the substrate/catalyst ratio resulted in a significant enhancement of activity and TONs of 634 and 849 were obtained at high DMM selectivity. Moreover, a further increase of formic acid concentration to 3.4 mmol/mL resulted in a yield of 47% and a high TON of 1076 (Table 2, entry 4). However, at this concentration of formic acid the formation of MF is dominating the reaction cascade, resulting in decreased DMM selectivity and a MF yield of 24% (Table 2, entry 4). Any further increase of the formic acid concentration (4.0 and 4.9 mmol/mL) did not result in increased yield and TON (Table 2, entries 4–6). Instead, DMM yield/TON decreased to 35%/924 and 23%/758, whereas the MF yield increased to 41 and 51% (Table 2, entries 5 and 6).

The influence of the initial formic acid concentration on the reactivity and selectivity of the reaction is illustrated in Figure 2. The reaction of formic acid towards DMM proceeds nearly constant up to an initial formic acid concentration of 3.4 mmol/mL. Beyond this concentration, a clear decrease in the DMM yield can be detected, depicting the limitations of the

![Figure 1](https://example.com/figure1.png)
developed catalyst system with respect to the formic acid concentration.

Further mechanistic details of the cascade transformation should be obtained with selected labelling studies. In an additional set of experiments, the catalyst system \([\text{Ru(triphos)}(\text{tmm})]/\text{Al(OTf)}_3\) was initially applied in presence of non-labelled formic acid and \(^{13}\text{CD}_2\text{OD}\). The NMR analysis revealed that the MF intermediate and the final product DMM have the \(^{13}\text{C}\)-label incorporated only in the methyl groups, confirming their origin from methanol and the generation of the CH\(_2\)O-unit of the DMM product from formic acid and H\(_2\) (Scheme 2, A; see also supporting information). Next, deuterium-labeled formic acid in presence of methanol as substrates resulted in the selective formation of the DMM product with a single deuterium atom (90% selectivity, Scheme 2, B). Similar results were observed when using mono-deuterated methanol as the C1 source, affording the DMM product with single deuterium atom in more than 90% selectivity (Scheme 2, C).

Moreover, the labelling results and the absence of any oxidative pathways for methanol, clearly corroborate the origin of the methylene group of DMM from formic acid. Consequently, a sequential pathway of DMM formation starting from methanol, formic acid and H\(_2\) can be proposed. First, MF is formed via the Lewis acid-catalyzed esterification reaction of formic acid and methanol. The subsequent reduction of the MF to methoxy methanol (MM) is mediated by the Ru-triphos system, followed by acetalization of the formed MM with methanol, yielding the target product DMM (Scheme 3). Consequently, the reaction sequence with formic acid to DMM is from a mechanistic perspective in agreement with the previously observed reaction mechanism of CO\(_2\) to DMM.

Having the initial optimal conditions in hand, the scope of the new reaction with a selection of structurally different alcohols for the synthesis of dialkoxymethanes was investigated (Table 3). Using the formic acid approach, the reaction of ethanol afforded the target product diethoxymethane (DEM) with a TON of 526, using a 3.1 mmol/mL concentration of formic acid (Table 3, entry 1). Other alcohols performed even better at formic acid concentrations of 1.5-1.8 mmol/mL (Table 3, entries 2-6 and supporting information). In detail, the use of 1-butanol yielded dibutoxymethane diether (DBM) with a high TON of 318 (Table 3, entry 2). Using 1-octanol and 1-decanol afforded the corresponding dialkoxymethane products DOM and DDM in TONs of 222 and 134 respectively (Table 3, entries 3 and 4). The secondary isopropanol resulted in the formation of di-isopropoxymethane diether (DiPM) with a TON of 173 (Table 3, entry 5). In addition, also benzyl alcohol could be used as substrate, yielding dibenzoxymethane diether (DBnM) with a TON of 198 (Table 3, entry 6).

In conclusion, in the present study a catalytic approach to dialkoxymethanes utilizing formic acid as source for the methylene unit could be developed. The catalyst system, comprising the combination of \([\text{Ru(triphos)}(\text{tmm})]/\text{Al(OTf)}_3\) and the Lewis acid \(\text{Al(OTf)}_3\), enabled the synthesis of selected acetals in TONs up to 1076. Mechanistic investigations and labelling studies revealed a catalytic cascade reaction, starting from formic acid via the respective formate ester, methoxy methanol to the dialkoxy-methane product DMM. In comparison to the established

![Scheme 2](image_url)

**Scheme 2.** Isotopic labeling observed by NMR spectroscopy for the \([\text{Ru(triphos)}(\text{tmm})]/\text{Al(OTf)}_3\)-catalyzed synthesis of DMM starting from: A) formic acid and \(^{13}\text{CD}_2\text{OD}\), B) \(\text{DCO}_2\text{D}\) and methanol, or C) \(\text{CH}_3\text{OCDO}\) and methanol.

![Scheme 3](image_url)

**Scheme 3.** Proposed reaction pathway for the \([\text{Ru(triphos)}(\text{tmm})]/\text{Al(OTf)}_3\)-catalyzed synthesis of DMM using methanol and formic acid.

| Entry | Formic acid [mmol/mL] | ROH | DAM [TON][b] |
|-------|-----------------------|-----|--------------|
| 1     | 3.1                   |     | DEM (526)    |
| 2     | 1.7                   |     | DBM (318)    |
| 3     | 1.5                   |     | DOM (222)    |
| 4     | 1.6                   |     | DDM (134)    |
| 5     | 1.7                   |     | DiPM (173)   |
| 6     | 1.8                   |     | DBnM (198)   |

[a] Reaction conditions: \([\text{Ru(triphos)}(\text{tmm})]\) (3 \(\mu\)mol), \(\text{Al(OTf)}_3\) (25 \(\mu\)mol), formic acid (x mmol/mL), ROH (2 mL), H\(_2\) (80 bar), 18 h, 80 °C; [b] Turnover numbers TONs were determined by NMR using mesitylene as internal standard.

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**Table 3.** Ruthenium-catalyzed synthesis of dialkoxymethanes (DAM) using selected alcohols.© 2020 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA
pathway via CO₂, the more reactive and readily available formic acid may streamline future reaction engineering concepts. Current investigations are targeted towards this process challenge and the optimization of the established catalyst lead structure and reaction conditions.

Experimental Section

General procedure for the synthesis of dimethoxymethane DMM from methanol, formic acid and H₂: A 2.0 mL solution of [Ru(triphos)(tmm)] (2.34 mg, 3 μmol) and Al(OTf)₃ (1.18 mg, 25 μmol) in methanol was prepared under argon atmosphere in a Schlenk tube containing a stirring bar. After stirring for 5 minutes, the solution was transferred to a carefully degassed and dried 20 mL stainless-steel autoclave via cannula. The corresponding formic acid amount was then added to the autoclave via cannula. The autoclave was then pressurized at room temperature with 80 bar H₂. The reaction mixture was agitated with a magnetic stir bar and heated to 80 °C using a preheated aluminum cone. After 18 h the autoclave was cooled in an ice bath and then carefully vented. Turnover number (TON) of DMM in solution was analyzed via ¹H-NMR using mesitylene as internal standard.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] J. Klankermayer, S. Wesselbaum, K. Beydoun, W. Leitner, Angew. Chem. Int. Ed. 2016, 55, 7296.
[2] M. G. Mura, L. D. Luca, G. Giacomelli, A. Porcheddu, Adv. Synth. Catal. 2012, 354, 3180; b) S. Savourey, G. Lefevre, J.-C. Berthet, T. Cantat, Chem. Commun. 2014, 50, 14033; c) W. Supronowicz, I. A. Ignatyev, G. Loli, A. Wolf, L. Zhao, L. Mlezko, Green Chem. 2015, 17, 2904; d) K. Sordalaks, C. Tang, L. K. Vogt, H. Junge, P. J. Dyson, M. Beller, G. Laurenczy, Chem. Rev. 2018, 118, 372.
[3] a) D. J. Drury, in Kirk-Othmer Encyclopedia of Chemical Technology, John Wiley & Sons, Inc., New York, 2000; b) W. Reutemann, H. Kieczka, in Formic Acid. Ullmann’s Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, 2005; c) H.-J. Arpe, Industrial Organic Chemistry, Wiley-VCH, Weinheim, 2010; d) http://www.oxfa.eu/en/, accessed on 09.11.2019.
[4] a) I. Yoshio, H. Itoshii, S. Yoshiyuki, H. Harukichi, Chem. Lett. 1976, 5, 863; b) E. Graf, W. Leitner, J. Chem. Soc. Chem. Commun. 1993, 1465; d) W. Leitner, Angew. Chem. Int. Ed. 1995, 34, 2207; e) D. Preti, C. Resta, S. Squarcialupi, G. Fachinetti, Angew. Chem. Int. Ed. 2011, 50, 12551; f) F. Zou, J. M. Cole, T. G. J. Jones, L. Jiang, Appl. Organomet. Chem. 2012, 26, 546; g) W. Leitner, U. Hintermair, S. Wesselbaum, Rheinisch-Westfälische Technische Hochschule Aachen, Germany - 2012. p. 31pp; Chemical Indexing Equivalent to 157:201438 (DE); h) B. G. Schieweck, N. F. Westhues, J. Klankermayer, Chem. Sci. 2019, 10, 6519; i) N. F. Westhuess, M. Belleflamme, J. Klankermayer, ChemCatChem 2019, 11, 5267.
[5] a) M. Berliner, K. Belecki, in Org. Synth., Vol. 84, Wiley-VCH, Weinheim, 2006; b) J. Burger, M. Siegert, E. Ströfer, H. Hasse, Fuel 2010, 89, 3315; c) B. Lumpp, D. Rothe, C. Pastötter, R. Lämmerner, E. Jacob, MTZ worldwide eMagazine 2011, 72, 34; b) D. Lumpp, D. Rothe, C. Pastötter, R. Lämmerner, E. Jacob, MTZ worldwide eMagazine 2011, 72, 34; e) J. Burger, E. Ströfer, H. Hasse, Chem. Eng. Res. Des. 2013, 91, 2648; f) A. Omari, B. Heuser, S. Pischinger, Fuel 2017, 209, 232; g) A. Peter, S. M. Fehr, V. Dübber, D. Himmel, I. Lindner, E. Jacob, M. Ouda, A. Schaadt, R. J. White, H. Scherer, W. R. Kroog, Angew. Chem. Int. Ed. 2018, 57, 9461.
[6] a) S. Deutz, D. Bongartz, B. Heuser, A. Kartelhon, L. Schulze Langhorst, A. Omari, M. Walters, J. Klankermayer, W. Leitner, A. Mitsos, S. Pischinger, A. Bardow, Energy Environ. Sci. 2018, 11, 331; b) B. Lehrheuer, F. Hoppe, K. A. Heuffer, S. Jacobs, H. Minwegen, J. Klankermayer, B. Heuser, S. Pischinger, Proc. Combust. Inst. 2019, 37, 4691.
[7] a) G. Reuss, W. Disteldorq, A. O. Gomer, A. Hilt, in Ullmann’s Encyclopedia of Industrial Chemistry, Wiley-VCH, 2000; b) S. Sato, Y. Tanigawa, ASAHI CHEM IND Co. Ltd., Japan, JP2000109443 A, Japan, 2000; c) H. Hasse, J. O. Drunsel, J. Burger, U. Schmidt, M. Renner, S. Blagov, Ineos Paraform GmbH & Co. Kg, Germany, US20140187823 A1, US, 2014; d) M. Li, Y. Long, Z. Deng, H. Zhang, X. Yang, G. Wang, Catal. Commun. 2015, 68, 46.
[8] a) K. Thenert, K. Beydoun, J. Wiesenthal, W. Leitner, J. Klankermayer, Angew. Chem. Int. Ed. 2016, 55, 12266; b) K. Beydoun, J. Klankermayer, Chem. Eur. J. 2019, 25, 11412; c) K. M. Thenert, Ph.D Thesis thesis, RWTH Aachen University (Aachen), 2018.
[9] M. Siebert, G. Krennrich, M. Seibich, A. F. Siegle, O. Trapp, Chem. Sci. 2019, 10, 10466.
[10] B. G. Schieweck, J. Klankermayer, Angew. Chem. Int. Ed. 2017, 56, 10854.
[11] a) S. Bontemps, L. Vendier, S. Sabo-Etienne, Angew. Chem. Int. Ed. 2012, 51, 1671; b) M. Rauch, Z. Strater, G. Parkin, J. Am. Chem. Soc. 2019.