

# Research and Development of the Catalytic Oxidation of Methylacrylate to 3,3-Dimethoxy Methyl Propionate

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## Abstract:

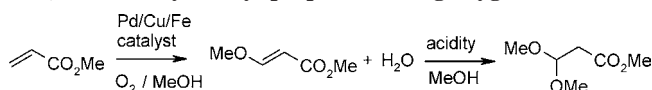
A selective synthesis of 3,3-dimethoxy methyl propionate has been developed using a green approach, in which the key step is a palladium-catalyzed oxidation of methylacrylate in methanol using oxygen as oxidant. The relationship between several reaction parameters including catalyst composition, oxygen pressure, substrate/solvent ratio, reaction temperature and reaction performance have been discussed. The data obtained in combination with data on explosion limits enabled successful scale-up to a 2 L scale, giving the desired product in 82% yield and 99% purity. Special attention is paid to catalyst activity, catalyst cost contribution, solvent recovery and safety. The product is a valuable industrial fine chemical for the synthesis of pharmaceuticals, functionalized polymers and adhesives, as it contains a protected aldehyde functional group, an ester functional group and an activated methylene function.

## Introduction

We became interested in the synthesis of 3,3-dimethoxy methyl propionate because we think it has high potential as a synthetic building block in numerous chemical processes, due to the presence of a protected aldehyde functional group, an ester functional group and an activated methylene functional group. In fact, we have previously developed a route<sup>1</sup> for the synthesis of methyl cyanoacetate from 3,3-dimethoxy methyl propionate. Methyl cyanoacetate is a key intermediate in the synthesis of cyanomethyl methacrylate, which finds wide application in the adhesive industry.<sup>2</sup> We envisaged the synthesis of 3,3-dimethoxy methyl propionate by a Wacker-type oxidation of the cheap starting material methylacrylate, using methanol as solvent (Scheme 1).

This type of oxidation reaction is well established at the Mitsubishi Chemical Corporation in, for example, the oxidation of cyclohexene in glycols to give cyclohexanone ketals<sup>3</sup> and the oxidation of acrolein in 1,3-propanediol to give the corresponding propanedialdehyde diacetal.<sup>4</sup> A general procedure for the methylacrylate oxidation consists of reacting the substrate with a methanol solution containing palladium, copper and iron

## Scheme 1. Pd/Fe/Cu-catalyzed oxidation of methylacrylate to 3,3-dimethoxy methyl propionate using oxygen as oxidant



as catalyst components under oxygen or air pressure. Generally, the Wacker<sup>5</sup> oxidation combines the stoichiometric oxidation of an olefin by Pd(II) in aqueous solution with the reoxidation of Pd(0) *in situ* by molecular oxygen in the presence of copper salts. The overall reaction constitutes a palladium-catalyzed oxidation of olefins to aldehydes or ketones. In our case the reaction differs from conventional Wacker oxidation as reaction takes place in an alcohol as solvent.<sup>6</sup> The Pd(II) oxidizes the methylacrylate substrate to produce 3-methoxy methylacrylate, while being reduced to Pd(0). Under the acidic reaction conditions the 3-methoxy methylacrylate is only an intermediate and is quickly converted to 3,3-dimethoxy methyl propionate. Reoxidation of Pd(0) is achieved by Cu(II) oxidation as is similar to conventional Wacker oxidation. The Cu(I) which is formed can be reoxidized to Cu(II) by oxygen, but we have found it advantageous<sup>3</sup> to reoxidize the Cu(I) using Fe(III) and then to reoxidize the Fe(II) using oxygen as this is faster, enhancing the stability of the palladium catalyst. In principle, this oxidation of methylacrylate can be carried out in water, which would lead to the free aldehyde as product. However, aldehydes are very susceptible to overoxidation, leading to a decrease in product selectivity. By carrying this reaction out in alcohol solvents the aldehyde product is protected as an acetal, minimizing overoxidation. Not only is alcohol a good solvent for this reaction based on reactivity and miscibility, but also through the formation of protective acetals it has a positive effect on product selectivity.

This process makes use of a catalytic reaction and an environmentally friendly oxidant and fits nicely into the context of green chemistry. However, there are three key problems with this type of reaction: the danger of an explosion due to the oxygen-rich gas phase, the danger of runaway reactions due to

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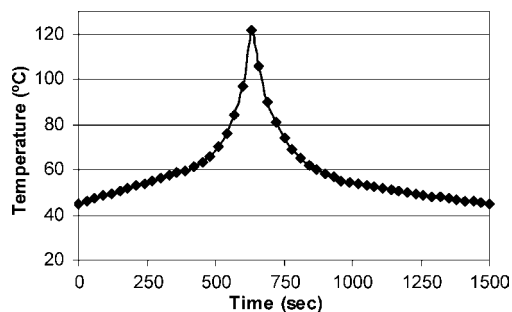
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**Chart 1.** Internal reaction temperature of the oxidation of methylacrylate to 3,3-dimethoxy methyl propionate against time, illustrating the exothermic nature of the reaction



the exothermic nature of the reaction and the above-mentioned overoxidation of the product, especially at high conversions.

While studying the palladium-catalyzed oxidation of methylacrylate in methanol using oxygen as oxidant, to form 3,3-dimethoxy methyl propionate, we encountered all three of these problems. The initial experiments were conducted using pure oxygen, and for the sake of safety we were constrained to using small robust autoclaves equipped with bursting discs. High substrate and catalyst concentrations resulted in the internal reaction temperature rising considerably faster than the temperature of the external heating source due to the exothermic nature of the oxidation. This effect was exacerbated by Teflon inserts used to protect the autoclave against the corrosive catalyst solution. Containing the reaction mixture in a good insulator such as Teflon led to runaway reactions with internal temperatures exceeding the external heating bath by up to 80 °C (see Chart 1).

In this particular experiment methylacrylate was reacted with the Pd/Cu/Fe catalyst at 0.9 MPa oxygen pressure while heating the autoclave at 45 °C. In about 10 min the internal reaction temperature reached 120 °C. At this point the reaction started to stop as oxygen depletion led to palladium-catalyst deactivation by palladium-black formation. In addition, product selectivity was decreased due to overoxidation and other side reactions. Experiments like this on large scale could very easily lead to dangerous situations involving pressure buildup and explosions.

In this contribution we report our investigations of the relationships between reaction parameters such as catalyst composition, catalyst ratio, oxygen pressure, temperature, catalyst stability and product selectivity. Combining our understanding of these factors with data obtained concerning explosion safety, we successfully scaled the reaction up to 2 L scale. The reaction kinetics are in good agreement with our proposed mechanism, and this can be used to model different reaction conditions. We believe that we can use the model to scale up this process to 1000 tonnes per year.

## Results and Discussion

**Small-Scale Reaction Optimisation.** The first part of the optimization was to reduce the cost contribution of the catalyst to the price of the final product to a minimum. The conditions for catalyst optimization involved the oxidation of methylacrylate in a methanol solution containing a Pd/Cu/Fe catalyst at 70 °C and 0.2 MPa oxygen pressure while stirring at 1000 rpm on a 50 mL scale. The molar ratio of the reaction components was as follows; methylacrylate/ $\text{Na}_2\text{PdCl}_4$  = 40000, methanol/

**Table 1.** Minimization of the catalyst cost to the cost of 3,3-dimethoxy methyl propionate/ $\text{FeCl}_2$

Cu source	Fe source	Cu/Fe/Cl	Activity <sup>a</sup>	Cost/kg product <sup>a</sup>
$\text{CuCl}_2$	$\text{FeCl}_3$	1/1/5	0.23	8.44
$\text{CuCl}$	$\text{FeCl}_3$	1/1/4	1.00	1.85
$\text{CuCl}_2$	$\text{FeCl}_2$	1/1/4	1.04	1.92
$\text{Cu}$	$\text{FeCl}_3$	1/1/3	1.62	1.00
$\text{Cu}(\text{OAc})_2$	$\text{FeCl}_3$	1/1/3	1.62	1.51
$\text{CuCl}_2$	$\text{Fe}(\text{OAc})_2$	1/1/2	1.81	1.32
$\text{CuCl}_2$	$\text{FeSO}_4$	1/1/2	1.35	1.11
$\text{Cu}(\text{OAc})_2$	$\text{FeCl}_2$	1/1/2	2.27	1.09
	$2/3 \text{ FeCl}_3$			
$\text{Cu}(\text{OAc})_2$	$1/3 \text{ Fe}(\text{OAc})_2$	1/1/2	2.15	1.20

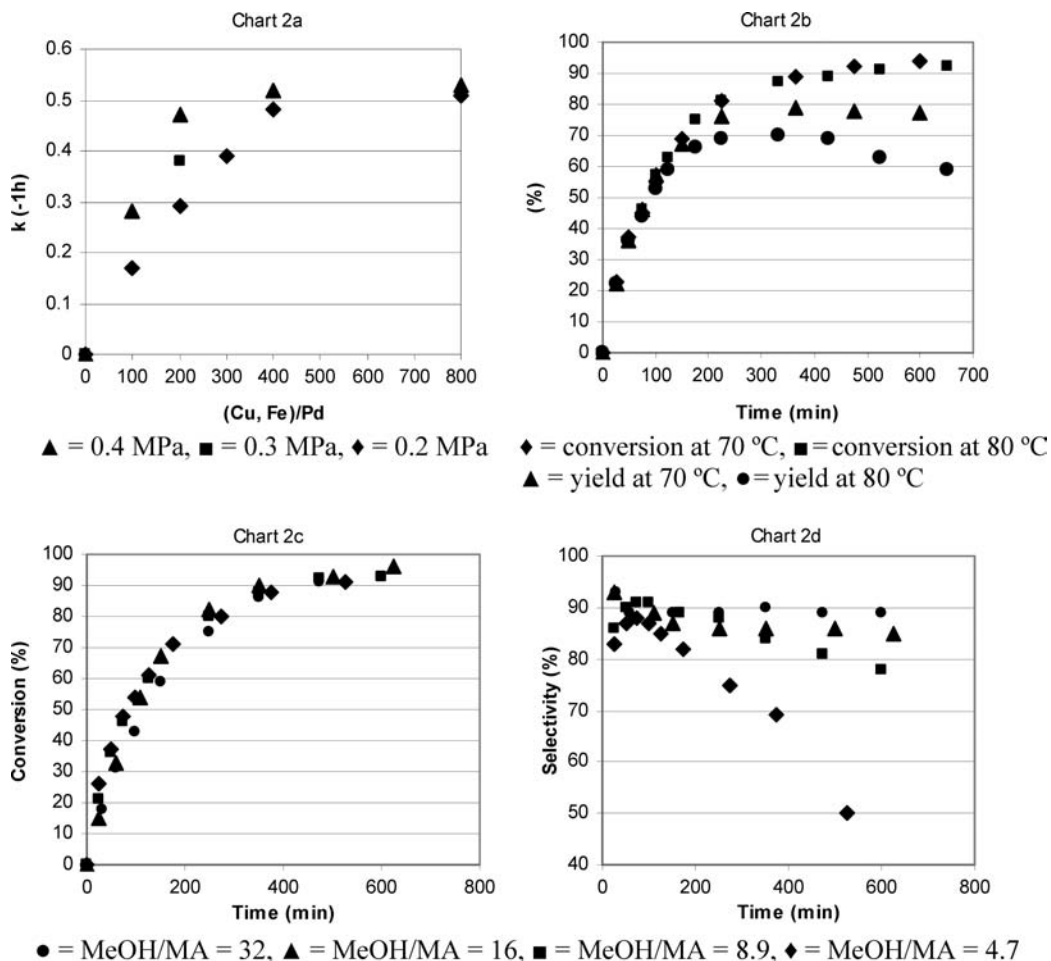
<sup>a</sup> Arbitrary unit.

methylacrylate = 8.9 and Pd/Cu/Fe = 1/230/230. Because the  $\text{Na}_2\text{PdCl}_4$  was used in such a small amount compared to the substrate and it is one of the cheapest palladium sources available, we decided not to investigate its contribution to the product cost price. The Cu and Fe cocatalyst on the other hand, are used in larger amounts and contribute significantly to product price (Table 1).

From the several Cu and Fe combinations used it can be seen that the activity of the system increases with decreasing amount of chloride anion. Taking the price of the catalyst components into consideration it appears that the combination of elemental copper and  $\text{FeCl}_3$  gives the lowest contribution to 3,3-dimethoxy methyl propionate cost price. The physical form of metallic copper used as catalyst component does not influence the reaction negatively. This is because the catalyst solution is prepared prior to use by mixing  $\text{FeCl}_3$  and metallic copper in methanol.  $\text{FeCl}_3$  is a strong enough oxidant to oxidize elemental Cu, causing it to dissolve. In all the future experiments we used the combination of  $\text{Na}_2\text{PdCl}_4$ ,  $\text{FeCl}_3$  and Cu as the catalyst combination.

In the previous experiment the Pd/Cu/Fe catalyst ratio of 1/230/230 was chosen arbitrarily. We investigated the effect of changing the Pd/Cu/Fe ratio on the reaction rate at different oxygen pressures. The conditions were as follows; Methylacrylate was oxidized in methanol to 3,3-dimethoxy methyl propionate at 70 °C using the  $\text{Na}_2\text{PdCl}_4$ ,  $\text{FeCl}_3$ , Cu catalyst combination. The Cu/Pd and Fe/Pd molar ratios were varied from 100 to 800, and reactions were done at oxygen pressures of 0.2 MPa, 0.3 and 0.4 MPa (Chart 2a). At (Cu, Fe)/Pd molar ratios of lower than 400 the reaction rate is strongly dependent on the oxygen pressure and catalyst ratio. In other words, under these conditions the reaction is first order in (Cu, Fe)/Pd ratio and oxygen pressure and zero order in palladium and substrate concentration. At (Cu, Fe)/Pd molar ratios higher than 400 the reaction rate is independent of the oxygen pressure. Under these conditions the reaction is zero order in (Cu, Fe)/Pd molar ratio and oxygen pressure, while it is first order in palladium and substrate concentration. This has significant implications for further development of this process as we now can keep high reaction rates even at low oxygen pressure, because the reaction is zero order in oxygen at (Cu, Fe)/Pd molar ratios of higher

**Chart 2.** Investigation of reaction parameters: (a) effect of catalyst composition on reaction rate at different pressures; (b) product selectivity at different reaction temperatures but with same reaction profiles; (c) conversion curves at different MeOH/MA ratios; (d) selectivities at different MeOH/MA ratios



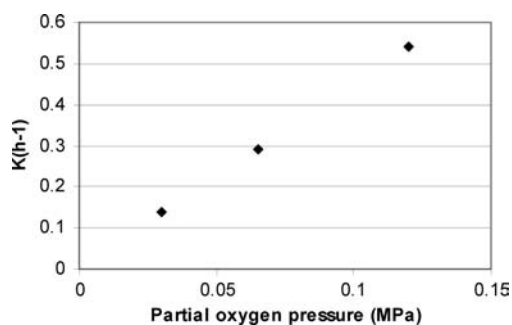
than 400. For example, using this high (Cu, Fe)/Pd molar ratio catalyst solution at an industrial scale would reduce the manufacturing capacity required. Furthermore, the catalyst performance will be less sensitive to fluctuations of partial oxygen pressure due to, for example, inefficient stirring. In the following experiments we will use  $\text{Na}_2\text{PdCl}_4/\text{FeCl}_3/\text{Cu}$  molar ratios of 1/500/500 using an oxygen pressure of 0.2 MPa.

An attempt was made to find the optimum temperature for this reaction through the comparison of reaction profiles measuring selectivity against time at different temperatures. This was done by careful adjustment of the methylacrylate/Pd ratio. It appeared that, when the methylacrylate/Pd ratio is decreased from 40000 to 25000 while decreasing the reaction temperature from 80 to 70 °C, the same conversion curve is obtained (Chart 2b).

For up to 60% methylacrylate conversion for both the 70 and 80 °C reactions, selectivity is nearly quantitative and the yield curve approximates the conversion curve. From 60% conversion to about 95% conversion selectivity to product starts to decrease in both cases, but the decrease in selectivity is more pronounced in the 80 °C experiment, leading to a product yield lower than 60% at 95% conversion. Product yield at 95% conversion in the case of the 70 °C reaction is above 75%. The reason for the decrease in selectivity at higher conversions can be explained by the equimolar coproduction of water in the

oxidation of methylacrylate to 3,3-dimethoxy methyl propionate. Under the acidic reaction conditions the intermediate 3-methoxyacrylate equilibrates with water and the hemiacetal, 3-methoxy-3-hydroxy methyl propionate. This hemiacetal is unstable under these reactions conditions and undergoes side reactions, which are primarily irreversible overoxidations. This occurs either on the hemiacetal itself or by deprotection to the free aldehyde followed by oxidation. All of these reactions rates will increase with temperature, but the irreversible nature of the oxidation will pull the equilibrium to overoxidized byproduct, reducing the yield of the desired product. Increasing the amount of methanol in the system should reduce hemiacetal formation, thereby blocking this overoxidation route and increasing the overall yield of the reaction. The results of variation of methanol/methylacrylate ratio on activity and selectivity are depicted in Chart 2c and Chart 2d, respectively. Oxidizing methylacrylate in a methanol solution containing a Pd/Cu/Fe/methylacrylate molar ratio of 1/500/500/25000 at an oxygen pressure of 0.2 MPa using different methanol/methylacrylate ratios does not show any differences in the conversion curves. As predicted, at the high conversion of 90% using a low methanol/methylacrylate ratio of 4.7 a drastic decrease in 3,3-dimethoxy methyl propionate selectivity is observed, falling as low as 50%. Increasing the methanol/methylacrylate ratio to 32 gives a selectivity of 90% at more than 94% conversion.

**Chart 3. Behavior of reaction rate with decreasing oxygen partial pressure at constant total pressure**



However, this high ratio of 32 makes the reaction very dilute and will result in very poor plant utilization. A methanol/methylacrylate ratio of 16 is sufficient for the large-scale experiments as selectivity drops just a few percent compared to the ratio of 32.

So far, all the experiments were conducted using pure oxygen under pressure, resulting in conditions where an explosion could occur. For the sake of safety we investigated bubbling with pressurized N<sub>2</sub>/O<sub>2</sub> mixtures with a Pd/Cu/Fe/methylacrylate molar ratio of 1/500/500/25000 at 70 °C. Reducing the total N<sub>2</sub>/O<sub>2</sub> pressure from 0.9 MPa to 0.29 MPa and simultaneously increasing oxygen concentration from 12.9% to 40% and consequently keeping the oxygen partial pressure constant at 0.116 MPa, gives a constant reaction rate of 0.58 h<sup>-1</sup>. Decreasing the oxygen partial pressure from 0.116 to 0.031 MPa by decreasing total pressure from 0.90 to 0.24 MPa with constant oxygen concentration of 12.9% led to a decrease in reaction rate from 0.54 to 0.28 h<sup>-1</sup>. A linear decrease in reaction rate is observed (Chart 3) when the total pressure is kept constant at 0.90 MPa and the total oxygen partial pressure is decreased from 0.12 to 0.03 MPa by reducing the oxygen concentration from 13 to 3.4%.

The linear decrease in reaction rate means that, even when the oxygen concentration is very low in the reaction solution, no deactivation of the palladium catalyst takes place. This is of major importance for larger-scale reactions where the N<sub>2</sub>/O<sub>2</sub> reaction mixture feed will have an oxygen concentration just below the explosion limit, but the outlet N<sub>2</sub>/O<sub>2</sub> mixture will be much lower in oxygen due to the consumption during the reaction. This outlet oxygen concentration must be high enough to ensure that active palladium catalyst is not deactivated by palladium black formation. The results from Chart 3 show us outlet gas oxygen concentrations of as low as 3% can be tolerated without deactivation of the catalyst.

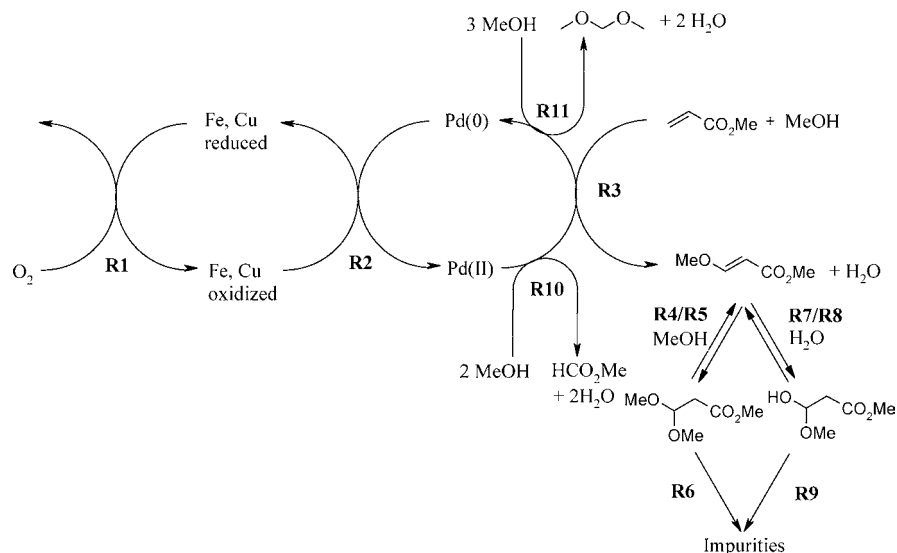
Explosion limits were determined experimentally on both a starting reaction mixture of 14% methylacrylate and 86% methanol and on a product mixture 1% methylacrylate, 73% methanol, 23% 3,3-dimethoxy methyl propionate and 3% water at 75 °C and a total gas pressure of 0.45 MPa. The result was for the starting reaction mixture no explosion could occur at oxygen percentages below 17.7%, and for the final reaction mixture the value was 13.8%.

**Large-Scale Methylacrylate Oxidation Reaction and Workup.** So far we have optimized the catalyst composition, temperature, pressure, methanol/methylacrylate ratio, and we know how we can carry the reaction out safely in terms of

explosion limits. The reaction could now be tested on a 2 L scale. The reaction was done by heating a 2 L mixture of methylacrylate in methanol (methanol/methylacrylate = 16) in a 3-L autoclave to 70 °C while feeding a N<sub>2</sub>/O<sub>2</sub> mixture (containing 13% oxygen) at 0.61 MPa and stirring at 1000 rpm. When the mixture was at reaction temperature, the reaction was started by injecting a 10 mL methanol solution containing the catalyst components (Na<sub>2</sub>PdCl<sub>4</sub>/Cu/FeCl<sub>3</sub> = 1/500/500, methylacrylate/Pd = 25000). The reaction was allowed to proceed for 9 h, after which the methylacrylate conversion was 95%, and 3,3-dimethoxy methyl propionate selectivity was 86%. The reaction mixture also contained minor amounts of methyl formate, dimethoxymethane and 3-methoxy methylacrylate. After cooling, 48.1 g 18.5 wt % solution of NaOH was added to neutralize the reaction solution. This was a 3-fold excess to ensure complete neutralization. Other bases, such as NaHCO<sub>3</sub> or Na<sub>2</sub>CO<sub>3</sub> could also effectively be used for this neutralization but suffer from the disadvantage of generating stoichiometric quantities of CO<sub>2</sub>. If the crude material is acidic, side reactions will occur during distillation, such as the demethoxylation of the 3,3-dimethoxy methyl propionate to form 3-methoxy methylacrylate. The reaction mixture (~1600 g) was transferred to a distillation flask, and a 726 g fraction containing methanol, methylacrylate, some water, methyl formate and dimethyl ether was distilled while heating from 42 to 50 °C at 160 mmHg. A second fraction weighing 324 g was distilled while heating from 50 to 61 °C at 160 mmHg which contained mainly methanol, some water and a small amount 3,3-dimethoxy methyl propionate. At this point, the contents of the flask separate into two layers. It proved to be beneficial to separate the water layer from the organic phase before continuing the distillation. Distilling the two-phase system gives a slight decrease in yield comparing to first-phase separation and then product distillation. Furthermore, distilling the two-phase system leaves an alkaline catalyst cake in the reaction flask which proved to be difficult to remove. Analysis of the 161 g water layer showed that it contained more than 95% of the used catalyst. In principle this catalyst can be reused after workup, but we did not attempt to investigate this as calculations show that on a 1000 tonnes/year scale that the financial benefit would be minimal. On the other hand, there may be an environmental case for recycling the catalyst in case this process goes into industrial production. After removal of the water layer the distillation of product was continued while increasing the temperature from 61 to 91 °C at 20 mmHg, giving a 20 g forerun product fraction, followed by a 207 g product fraction which boiled at 79.9–80.1 °C at 20 mmHg. The remaining catalyst layer in the flask was easily washed off with water. The mass balance of distillation of the total reaction mixture was 98.6%, while the mass balance of the combined forerun and main fraction of 3,3-dimethoxy methyl propionate was virtually 100%, giving an isolated yield of 82% based on methylacrylate charged. GC purity of the 3,3-dimethoxy methyl propionate was 99%. In this distillation 90% of methanol is recovered which can be distilled and be reused.

**Reaction Simulation Studies As Aid for Further Scale-up.** The reaction mechanism scheme of palladium-catalyzed oxidation of methylacrylate to 3,3-dimethoxy methyl propionate is presented in Scheme 2.

**Scheme 2.** Reaction mechanism of palladium-catalyzed oxidation of methylacrylate to 3,3-dimethoxy methyl propionate.



The palladium oxidizes the methylacrylate in the presence of methanol to form 3-methoxy methylacrylate and an equimolar amount of water with a reaction rate R3. The reduced Pd is reoxidized by the Fe/Cu cocatalyst with a reaction rate R2 giving a reduced Fe/Cu cocatalyst which is reoxidized by oxygen gas. The oxidized palladium catalyst can also form byproduct originating from the oxidation of two molecules of methanol to form methylformate or from the oxidation of three molecules of methanol to form dimethoxymethane. The 3-methoxy methylacrylate reacts either with a molecule of methanol to give the desired product 3,3-dimethoxy methyl propionate or with a molecule of water to form 3-hydroxy-3-methoxy methyl propionate. Both product molecules can lead to the formation of impurities, giving a decrease in product selectivity. It should be noted that the hemiacetal is less stable than the full acetal and is thus more prone to giving overoxidized byproduct. This proposed reaction mechanism in Scheme 2 was fitted with the obtained experimental data using the reaction equations belonging to the different reaction pathways together with the fitted values of activation energy and pre-exponential factors as are shown in Scheme 3. The reaction is 1.32 order in methylacrylate and 2.42 order in methanol.

The experimental data fit very well to the proposed reaction mechanism in Scheme 2. This gives us a good model for the palladium-catalyzed oxidation of methylacrylate to 3,3-dimethoxy methyl propionate. As an example the results from a reaction using a Pd/Cu/Fe/methylacrylate molar ratio of 1/500/500/25000 at 70 °C and oxygen pressure of 0.2 MPa at a methanol/methylacrylate ratio of 8.90 are compared with data generated by the model. (Chart 4).

We used the model to predict how the reaction would perform with different ratios of Cu and Fe to Pd. This showed that with a low ratio of Cu and Fe to Pd the reaction rate becomes first order with respect to the amount of Cu and Fe and oxygen and is zero order in palladium and methylacrylate. The reverse is true in the case of a high ratio of Cu and Fe. Hence, at high ratio of Cu and Fe to Pd the reaction rate is independent of the oxygen pressure. This means that under those conditions it may be possible to drop to a safe level of oxygen without deactivating the catalyst. The results from this simula-

tion prompted us to investigate in the laboratory and the results are shown in Chart 2a (above). This is a good example how the simulation of reaction conditions led to improvement of the design of the catalytic system. We showed that fitting our reaction kinetics with our proposed reaction mechanism gave good agreement with experimental data, and we are now able to simulate different reaction conditions, possibly using this tool for further scale-up to a 1000 tonnes/y process.

## Conclusion

In conclusion, we developed a safe synthetic route for the production of 3,3-dimethoxy methyl propionate by a palladium-catalyzed oxidation of methylacrylate in methanol using oxygen as oxidant. In 2 L scale experiments we obtained an 82% yield of 3,3-dimethoxy methyl propionate based on methylacrylate charged. Purity of the obtained product was 99%. Solvent and catalyst recovery were as high as 90% and 95%, respectively. This synthetic procedure will aid the development of adhesives, pharmaceuticals, agrochemicals and functionalized polymers.

## Experimental section

**General.** All reagents and solvents were obtained from commercial sources and were purified appropriately if necessary. Purity of starting materials and products and progress of reaction were determined by GC. GC was performed on a Varian Star 3600 gas chromatograph with a flame-ionization detector and a Chrompak CP Sil 5 CB wide-bore column (50 m × 0.53 mm) using nitrogen as carrier gas.

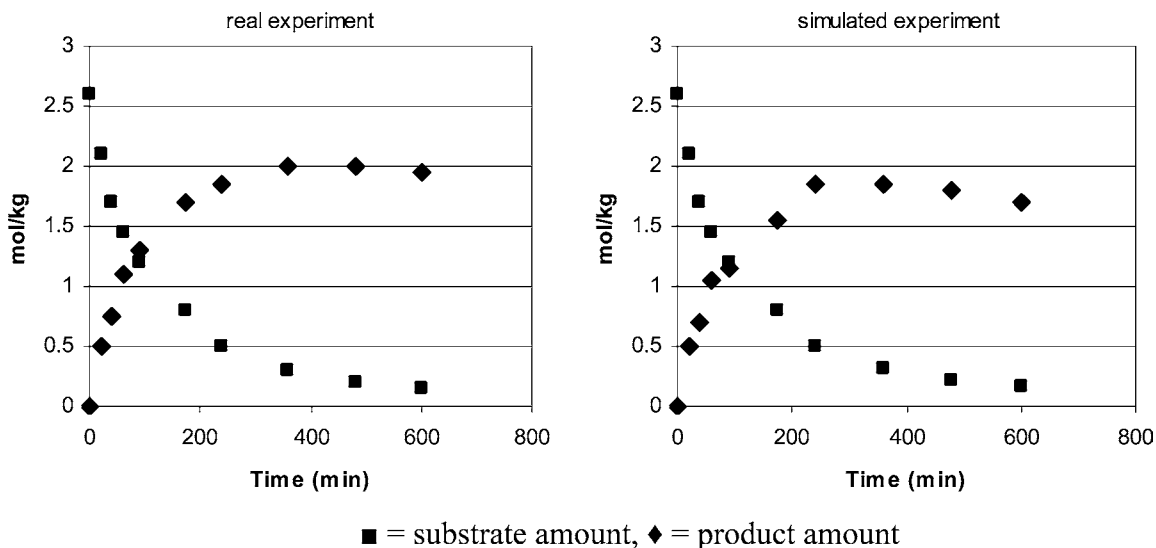
**Small-Scale Experiments.** A representative small-scale experiment is given below. The example chosen is a reaction using a Pd/Cu/Fe/methylacrylate molar ratio of 1/500/500/25000 at 70 °C and oxygen pressure of 0.2 MPa at a methanol/methylacrylate ratio of 8.90 (the experiment shown in Chart 4).

A 1.296 mg quantity of  $Na_2PdCl_4$  was dissolved in 0.26 g methanol, and 140.1 mg Cu and 358.2 mg  $FeCl_3$  were dissolved in 1.16 g methanol. The two solutions were combined and charged into an HPLC-pump with outflow into an autoclave. The Teflon-lined autoclave was charged with 9.486 g methy-

### Scheme 3. Reaction equations and the corresponding activation energies and pre-experimental factors

R1	$\text{Cu, Fe (reduced)} \rightarrow \text{Cu, Fe (oxidized)}$	
	$r1 = k1 \times [\text{Cu, Fe (red)}] \times [\text{PO}_2]$	$A = 3.14 \cdot 10^{+11} \text{ s}^{-1}, E_a = 71.8 \text{ kJmol}^{-1}$
R2	$\text{Cu, Fe (ox)} + \text{Pd(0)} \rightarrow \text{Cu, Fe (red)} + \text{Pd(II)}$	
	$r2 = k2 \times [\text{Cu, Fe (ox)}] \times [\text{Pd(0)}]$	$A = 4.95 \cdot 10^{+5} \text{ s}^{-1}, E_a = 0.0 \text{ kJmol}^{-1}$
R3	$\text{Pd(II)} + \text{MA} + \text{MeOH} \rightarrow 3\text{MAC} + \text{Pd(0)} + \text{H}_2\text{O}$	
	$r3 = k3 \times [\text{Pd(II)}] \times [\text{MA}]^{1.32} \times [\text{MeOH}]^{2.42}$	$A = 1.23 \cdot 10^{+10} \text{ s}^{-1}, E_a = 74.6 \text{ kJmol}^{-1}$
R4, R5	$3\text{MAC} + \text{MeOH} \leftrightarrow 33\text{MP}$	
	$r4 = k4 \times [3\text{MAC}] \times [\text{Cu, Fe}]$	$A = 7.17 \cdot 10^{+01} \text{ s}^{-1}, E_a = 0.5 \text{ kJmol}^{-1}$
	$r5 = k5 \times [33\text{MP}]$	$A = 4.2 \cdot 10^{+00} \text{ s}^{-1}, E_a = 0.4 \text{ kJmol}^{-1}$
R6	$33\text{MP} \rightarrow \text{IMP}$	
	$r6 = k6 \times [33\text{MP}]$	$A = 1.30 \cdot 10^{+01} \text{ s}^{-1}, E_a = 23.1 \text{ kJmol}^{-1}$
R7, R8	$3\text{MAC} + \text{H}_2\text{O} \leftrightarrow 3\text{H3M}$	
	$r7 = k7 \times [3\text{MAC}] \times [\text{H}_2\text{O}]$	$A = 8.59 \cdot 10^{+05} \text{ s}^{-1}, E_a = 0.0 \text{ kJmol}^{-1}$
	$r8 = k8 \times [3\text{H3M}]$	$A = 2.55 \cdot 10^{+06} \text{ s}^{-1}, E_a = 7.0 \text{ kJmol}^{-1}$
R9	$3\text{H3M} \rightarrow \text{IMP}$	
	$r9 = k9 \times [3\text{H3M}]$	$A = 8.93 \cdot 10^{+01} \text{ s}^{-1}, E_a = 10.4 \text{ kJmol}^{-1}$
R10	$2 \text{ MeOH} + 2 \text{ Pd(II)} \rightarrow \text{MF} + 2 \text{ Pd(0)} + 2 \text{ H}_2\text{O}$	
	$r10 = k10 \times [\text{Pd(II)}] \times [\text{MeOH}]$	$A = 5.15 \cdot 10^{+11} \text{ s}^{-1}, E_a = 78.0 \text{ kJmol}^{-1}$
R11	$3 \text{ MeOH} + \text{Pd(II)} \rightarrow \text{DMM} + \text{Pd(0)} + 2 \text{ H}_2\text{O}$	
	$r11 = k11 \times [\text{Pd(II)}] \times [\text{MeOH}]$	$A = 1.23 \cdot 10^{+17} \text{ s}^{-1}, E_a = 120.0 \text{ kJmol}$

Chart 4. Experimental data compared to simulated data



lacrylate, 0.5 g decane (internal standard) and 30 g methanol and heated to 70 °C while stirring at 1000 rpm under an oxygen pressure of 0.2 MPa (and kept at those conditions throughout the reaction). When the reaction mixture temperature had reached 70 °C, the catalyst solution was injected, the reaction was continued and samples were taken at stated times. GC analysis after 10 h reaction time showed 94.8% methylacrylate conversion with a 3,3-dimethoxy methyl propionate selectivity of 70%.

2. *Litre Scale.* A 31.8 mg quantity of  $\text{Na}_2\text{PdCl}_4$  was dissolved in 6.32 g methanol, and 3.44 g Cu and 8.79 g  $\text{FeCl}_3$  were dissolved in 28 mL methanol. The two solutions were combined and charged into an HPLC-pump with outflow into an autoclave.

A 233 g quantity of methylacrylate and 1363 g methanol were charged into a glass, 3 L autoclave, equipped with a condenser, catalyst feeding tube, gas bubbler and a heating jacket at 70 °C while dosing a 13%

O<sub>2</sub> 87% N<sub>2</sub> mixture at a total pressure of 0.61 MPa and stirring at 1000 rpm. When reaction temperature was reached, the catalyst solution was injected. The reaction was continued for 9 h under the conditions mentioned above. After cooling to room temperature, 48.1 g of 18.5 wt % aqueous NaOH was added, and 1596 g of the reaction mixture was transferred to a 3 L distillation flask. The flask was heated to 50 °C at 160 mmHg while a 726 g fraction containing methanol, methylacrylate, water, methyl formate and dimethyl ether was taken off. A second fraction of 324 g was obtained while heating from 50 to 61 °C at 160 mmHg which contained mainly methanol, some water and a small amount of 3,3-dimethoxy methyl propionate. Stirring was stopped, and 161.1 g water was

separated from the distillation mixture. Distillation was continued by heating to 91 °C at 20 mmHg pressure while collecting a forerun of 20.1 g of 3,3-dimethoxy methyl propionate, followed by a constant boiling fraction of 207.5 g of 3,3-dimethoxy methyl propionate at 79.9–80.1 °C at 20 mmHg. A 39.2 g quantity of residue remained in the flask, and it was easily dissolved in water. The trap between collection flasks and oil-pump contained a 95.5 g methanol/water mixture. Yield of the combined fractions was 82% with a purity of 99%.

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