

Pushing Boundaries—Selective Cooling Crystallization as Tool for Selectivity Compensation and Product Purification Using a Recyclable Pd/Xantphos Catalyst in the Methoxycarbonylation of Methyl 10-Undecenoate

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The homogeneously catalyzed methoxycarbonylation of methyl 10-undecenoate allows for the synthesis of dimethyl 1,12-dodecandioate as an interesting bio-based drop-in alternative for 1,12-dodecandioic acid as polymer building block. Although the benchmark catalyst system of Pd/1,2-bis((di-*tert*-butylphosphino)methyl)benzene and methane sulfonic acid is very active and selective, long-term stability over a potential catalyst recycling is limited. In this work, modifications of this catalyst system in terms of protonation of the ligand and its replenishment during recycling are first investigated, proving that the reaction system is tolerant against minor changes. Finally, the commercially available ligand Xantphos, featuring higher stability but comes with a rather low *l:b* selectivity of 70:30, is applied. However, through the application of cooling crystallization, 58 g product (52% isolated yield) with an overall purity of 94% is obtained from the crude reaction solution without further treatment and a \sum TON of 4000 after ten reaction runs, while catalyst loss into the product is low.

Practical Applications: Selective syntheses on the basis of renewable resources are a powerful tool for the production of value products in terms of green chemistry. Thereby, homogeneous transition metal catalysts are beneficial regarding selectivity. However, their separation and recycling are challenging due to their limited stability. The combination of a stable, commercially available catalyst with a selective purification method allows for isolation and purification from a crude reaction mixture without the need for any auxiliary or further purification steps. In this work, cooling crystallization is applied for subsequent purification of the linear diester dimethyl 1,12-dodecandioate. Thereby, a lower selectivity from the methoxycarbonylation reaction using the stable Xantphos ligand is compensated and combined with recycling of the homogeneous catalyst. Thus, the development of an integrated process covering a stable catalyst system in the reaction, and high selectivity in the purification is the key toward an efficient homogeneous catalyst recycling.

1. Introduction

In times of raising awareness of climate change and raw material shortage, the aim for sustainability is more important than ever before. In terms of Green Chemistry, application of renewable resources is inevitable for a sustainable value chain. To increase the proportion of renewable resources, the synthesis of drop-in alternatives to fossil resource-based materials is promising. Especially long-chained, bifunctional linear monomers for polycondensates are attractive.^[1] In principle, they are available via homogeneously catalyzed functionalization of unsaturated oleochemicals,^[2,3] that combine unsaturated carbon chains with acid/ester moieties. An example would be methyl 10-undecenoate (C₁₁-ME), which is available from pyrolysis of methyl ricinoleate, whose corresponding acid is the main compound of castor oil.^[4] Due to its terminal, well accessible double bond, methyl 10-undecenoate can easily undergo carbonylation, methoxycarbonylation, respectively, to form dimethyl 1,12-dodecandioate (*l*-C₁₂-DME), a potential bio-based diester.^[5] This α,ω -diester is an alternative to the industrially relevant 1,12-dodecandioic acid, widely used for manufacturing polyesters and polyamides such as nylon 6.12 from condensation with hexamethylenediamine. The industrial process for the synthesis of 1,12-dodecandioic acid is based on fossil resources: In a first step, butadiene is trimerized to 1,5,9-cyclododecatriene (CDT). Afterward, CDT is hydrogenated and oxidized resulting in 1,12-dodecandioic acid (Figure 1).^[6]

The homogeneously catalyzed methoxycarbonylation, also of oleocompounds, was first reported in the 1950s by Reppe^[7] and has developed to one of the most important carbonylation reactions since then. In 1973, the carbonylation of renewable resources was reconsidered in terms of potential industrial importance.^[8] Thereby, the homogeneous transition metal catalyst plays a decisive role, allowing for a high selectivity toward the

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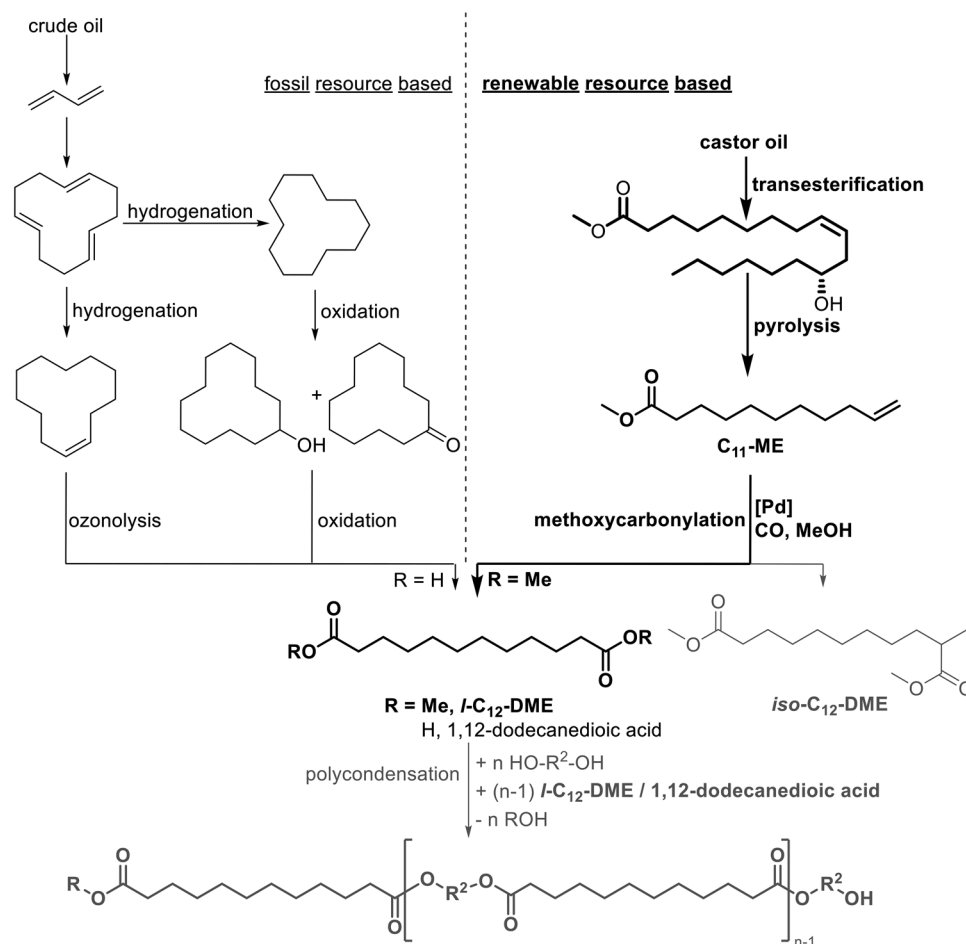


Figure 1. Methoxycarbonylation of C₁₁-ME as sustainable alternative to fossil resource-based synthesis of 1,12-dodecandioic acid and follow-up polycondensation thereof.

linear product resulting in reduction of waste at relatively mild conditions.

Among several transition metal catalysts, Pd-based catalyst systems are most active and relevant in the methoxycarbonylation.^[9] In combination with the ligand 1,2-bis((di-*tert*-butylphosphino)methyl)benzene (1,2-DTBPMB) and methane sulfonic acid (MSA) as stabilizer, the catalytic system is industrially applied in the “Alpha process” by Lucite (now part of Mitsubishi Chemical) for the synthesis of methyl propanoate from ethene as the first step in the synthesis of methyl methacrylate. Due to its success story, which we have recently reviewed,^[10] this catalyst system was successfully extended to a wide range of substrates, including several longer chained alkenes and unsaturated acids and esters.^[11] Substrates based on renewable oleochemicals that have been successfully methoxycarbonylated include triglycerides,^[12–15] fatty acids and fatty acid methyl esters,^[16] such as C₁₁-ME.^[5] Although the homogeneous Pd-catalyst is excellent

in terms of chemo- as well as regioselectivity to the desired linear product, its separation from the product and the recycling of the active catalyst species are challenging but required for high product quality regarding purity. In addition, the Pd-based catalyst is the most expensive compound in the reaction system. Therefore, reducing the amount of catalyst is not sufficient, but reusing and recycling is crucial for an economic potential process. The classical approach for recycling of a catalyst is product distillation and recycle of the heavies, such as the catalyst. This is also applied in the Alpha process toward separation of methyl propanoate.^[17] However, distillation is not feasible for separation of high boilers such as long chain fatty acids and esters. So far, other approaches for catalyst recycling in the alkoxy-carbonylation of several longer chained substrates have been reported,^[18] including, for instance, Wang-type polymeric sulfonic acids. These were used as Pd-resin in the hydroxycarbonylation and recycled for at least three times, however resulting in a reduced yield.^[19] Brønsted acid ionic liquids (BAILs)^[20] and supported ionic liquid phase technology (SILP)^[21] were found to enable recycling of the Pd/1,2-DTBPMB catalyst in the methoxycarbonylation of ethylene. However, ethylene is the simplest substrate, and alkoxy-carbonylation occurs much faster and at lower reaction temperature than for longer chained substrates,

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allowing for short-time thermal catalyst stress. Therefore, recycling is facilitated.

In contrast, longer chained, less polar substrates, such as fatty acid methyl esters, offer a promising solubility behavior in terms of catalyst recycling that can be taken advantage of for the application of a thermomorphic multiphase system (TMS).^[22] Regarding methoxycarbonylation of methyl 10-undecenoate, a TMS can be formed through addition of nonpolar dodecane.^[23–25] Principally, successful Pd/1,2-DTBPMB catalyst recycling was shown but activity decreased by 50% and finally, precipitation of Pd black was observed. Refreshment of MSA is necessary after each recycling step due to loss into the product phase and a high sensitivity of the catalyst against varying acid concentration.^[23]

Compared to this benchmark system, a Pd/(9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) system, known as Pd/Xantphos, leads to higher activities and robustness, but the desired high linear selectivity is drastically reduced and formation of the *iso*-product dimethyl 2-methylundecanedioate (*iso*-C₁₂-DME) and further branched diesters (*b*-C₁₂-DME) is increased.^[24] While rate-determining methanolysis is favored in a nonpolar solvent, catalyst activation and product dissociation is enhanced in a polar solvent.^[26] However, any additive should be avoided in terms of green chemistry. Hence, a biphasic approach for methoxycarbonylation of 1-dodecene as model substrate was investigated using SulfoXantphos as ligand to facilitate immobilization of the catalyst complex in the polar methanol phase. Thereby, water is mandatory to reduce catalyst loss and can be considered a green additive. But furthermore, octane is added to ensure stable phase separation.^[27] Although this approach was transferred to miniplant scale, chemo- and regioselectivity with this catalyst system were limited to 80%.^[28] Both approaches, TMS and biphasic system, are successful to a certain extent but they suffer from the need for organic additives and the dependence on the suitable catalyst system, so that a compromise between recyclability and selectivity must be found. Furthermore, both the linear and the branched product occur in the same phase after the reaction, so that further purification is required.

In contrast, our group investigated cooling crystallization as a recycling approach for homogeneous catalyst recycling, the efficiency of which is not depending on the catalyst system but on the product's solubility behavior.^[29–31] Crystallization is especially used for purification of pharmaceuticals. In cooling crystallization, the desired crystals start to form upon temperature-dependent supersaturation, followed by crystal growth.^[32] Since solubility strongly depends on the chemical structure, each compound crystallizes at a certain concentration and temperature. Thus, the method can be used to selectively crystallize one desired compound to separate, and isolate respectively, it from a reaction solution. A foundation for this concept was laid in 2006, when a procedure for the preparation of adipic acid from pent-4-enoic acid via hydroxycarbonylation using Pd/1,2-DTBPMB was patented.^[33] Thereby, the product was found to precipitate upon cooling the reaction mixture and could easily be filtered off. The concept was extended and carried out on 100 g scale with excellent selectivity.^[34] Recently, we described a strategy for the iterative improvement to design an integrated process, covering both, reaction and crystallization, to increase catalyst productivity and obtain a pure product while all other compounds, such as nonconverted substrate, side products, and the catalyst remain

in the mother liquor.^[35] Thereby, methoxycarbonylation of C₁₁-ME was applied as a model reaction. The general feasibility of the concept was shown using the commercially available catalyst system of Pd₂(dba)₃ as a precursor, 1,2-DTBPMB as a ligand, and MSA as cocatalyst, which is known for its outstanding selectivity toward linear ester products.^[10] Although highly stable in the alpha process, stability of this catalyst system is limited in methoxycarbonylation of other substrates than ethene,^[10] as precipitation of Pd black is observed during recycling.^[35] Therefore, modifications of the catalyst system with a focus on the ligand having a significant influence on selectivity might result in improved stabilization. Thus, replenishment of ligand or application of other ligands might be beneficial in terms of catalyst stability. Although most commercial ligands cannot compete with 1,2-DTBPMB in terms of linear selectivity, resulting in the formation of more waste side products, the tool of selective product crystallization would compensate this limitation, since the linear product is crystallized selectively. Hereby, remaining side products in the mother liquor must be considered. However, the process can still be economic, if long-term stability of the catalyst is reached and if side products eventually find another application.

In this work, we aim to increase catalyst stability in the methoxycarbonylation of C₁₁-ME (Figure 2) by modifying the catalyst system. Thereby, we investigate the effect of replenishment of ligand and apply the diprotonated ligand 1,2-DTBPMBH₂(Otf)₂, which was shown efficient for (re)activation of Pd⁰.^[36] Finally, our focus will be on the application of Xantphos^[37] as a more stable ligand, making use of the tool of selective product crystallization to obtain a pure, linear diester product *l*-C₁₂-DME even from a less selective catalyst in the methoxycarbonylation.

2. Results and Discussion

In our previous recycling study, formation of Pd black was observed during catalyst recycling after each reaction run. It is also known that the catalyst system of Pd/1,2-DTBPMB is very sensitive against minor changes in MSA concentration. However, MSA seems to deactivate due to esterification or decomposition.^[24] Thus, our interest was in the correlation of concentration of MSA and both, catalyst productivity and stability. Therefore, we screened methoxycarbonylation of C₁₁-ME and different MSA:Pd ratios (Figure 3).

The higher the MSA:Pd ratio, the lower the stability of the catalyst, measured as recovery in the reaction solution. Interestingly, this is contrary to catalyst productivity, which is highest at a ratio of 35:1 to 50:1. With our setup (see the Supporting Information for details) equipped with a dropping funnel with pressure compensation and a gas reservoir with pressure sensor, we monitored CO pressure in the reservoir over time, corresponding to conversion of C₁₁-ME. Figure 4 shows the reaction profile at different MSA:Pd ratios and in comparison, the profile using the protonated ligand as discussed later on.

The reaction profile of methoxycarbonylation using an MSA:Pd ratio of 50:1 indicates catalyst deactivation after not more than 15 h, since there is no significant increase in conversion afterwards. Similarly, using a ratio of 200:1 results in a significantly reduced increase of conversion after 2.7 h. Thus, we assume that catalyst deactivation toward Pd⁰ happens earlier at

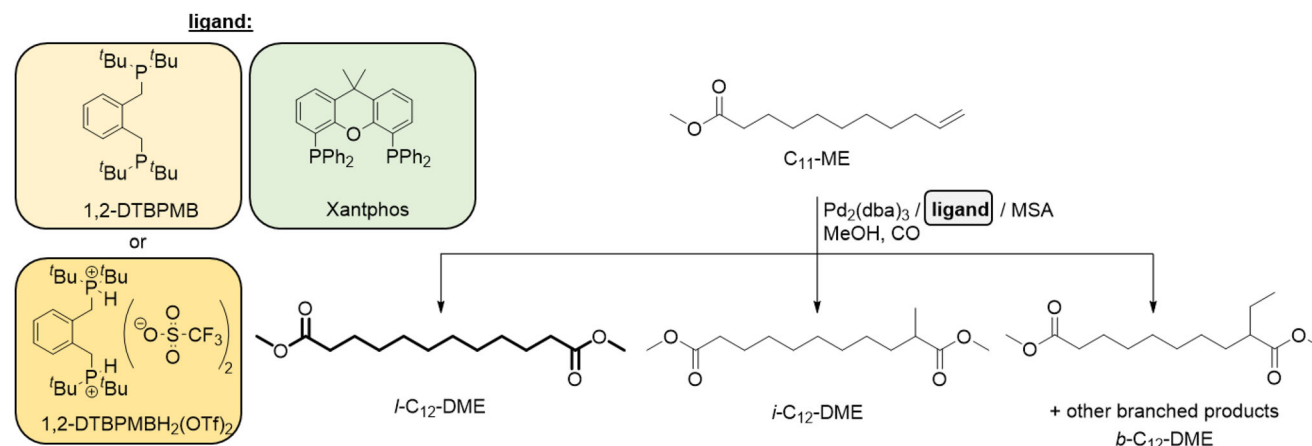


Figure 2. Methoxycarbonylation of methyl 10-undecenoate.

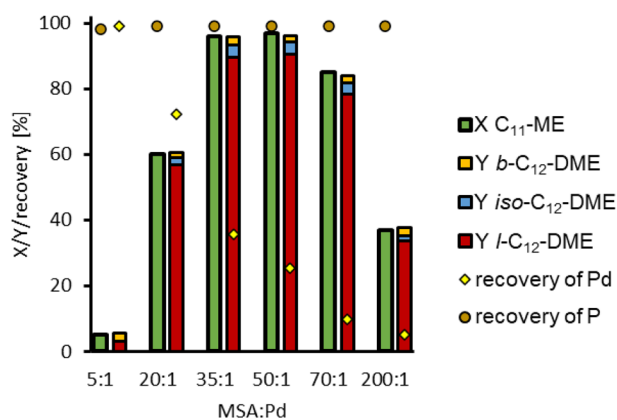


Figure 3. Effect of MSA: Pd ratio on catalyst productivity and stability in the methoxycarbonylation of C₁₁-ME.

Reaction conditions: C₁₁-ME (33 mmol), Pd₂(dba)₃ (0.05 mol%)/Pd:substrate 1:1000, 1,2-DTBPMB (1.75 mol%); 1,2-DTBPMB: Pd₂(dba)₃ 35:1, MSA, MeOH (48 g), T = 95 °C, t = 20 h, p(CO) = 30 bar. Conversion (X) and yield (Y) were determined via GC-FID-analysis using n-dodecane as internal standard. Pd/P recovery was determined in solution via ICP-OES.

a higher MSA: Pd ratio, although MSA is generally required for the formation of the active Pd species. This would also explain why conversion is high at a ratio of 35:1/50:1, although recovery of Pd is relatively low: deactivation occurs later in the process, when conversion is almost complete already. We conclude that catalyst stability and productivity are contrarily depending on the Pd:MSA ratio, which is an issue for catalyst recycling. Our, so far, optimized MSA: Pd ratio of 35:1 results in high catalyst productivity, but stability at a reaction time of 20 h is limited, so that less active catalyst can be recycled, resulting in lower conversion in the recycling run. Hence, our interest is in a modification of the catalyst system that allows for higher long-term stability which is beneficial during catalyst recycling.

Due to the described ability of the diprotonated ligand 1,2-DTBPMBH₂(OTf)₂ to reactivate Pd black,^[36] we investigated its application in a catalyst recycling (Figure 5), using our optimized reaction and crystallization conditions, that we have recently published.^[35] Thereby, we first replaced 50% of 1,2-DTBPMB by

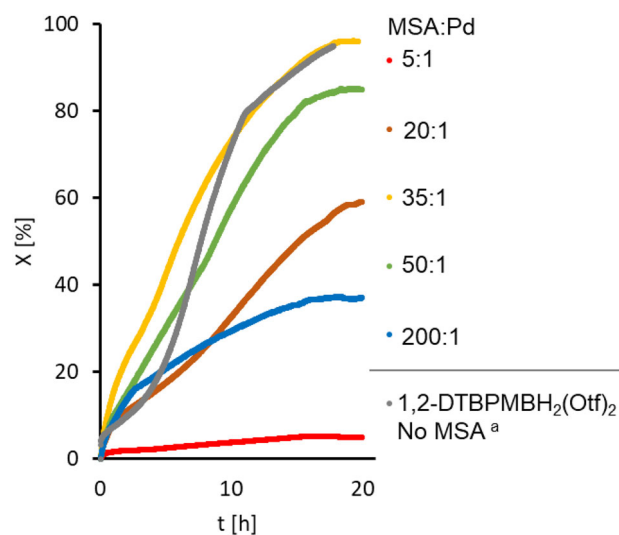


Figure 4. Reaction profile of methoxycarbonylation of C₁₁-ME depending on MSA: Pd ratio and with protonated ligand.

Reaction conditions: C₁₁-ME (33 mmol), Pd₂(dba)₃ (0.05 mol%)/Pd:substrate 1:1000, 1,2-DTBPMB (1.75 mol%); 1,2-DTBPMB: Pd₂(dba)₃ 35:1, MSA, MeOH (48 g), T = 95 °C, t = 20 h, p(CO) = 30 bar.^a protonated ligand 1,2-DTBPMBH₂(OTf)₂ (1.75 mol%). CO gas uptake is monitored and converted to X using the conversion determined from GC-FID analysis.

the diprotonated ligand, still having 50% MSA in the system, compared to our optimized conditions. The reaction time was set to 10 h, to reduce deactivation of the catalyst at reaction temperature.

Similar to the catalyst system comprising of 1,2-DTBPMB as the sole ligand, the catalyst was remained active over five recycling runs, and six runs in total, respectively. Thereby, a ΣTON of 5010 (4600)^[35] was reached regarding *l*-C₁₂-DME and a ΣTON of 5280 (5200)^[35] regarding C₁₂-DME (all isomers), respectively, which is similar to the result upon application of the unprotonated ligand. 35 g of *l*-C₁₂-DME could be isolated, corresponding to an isolated yield of 67%. This is slightly more than in our previous work (62%),^[35] which might be due to the improved selectivity when using the protonated and diprotonated ligand in a

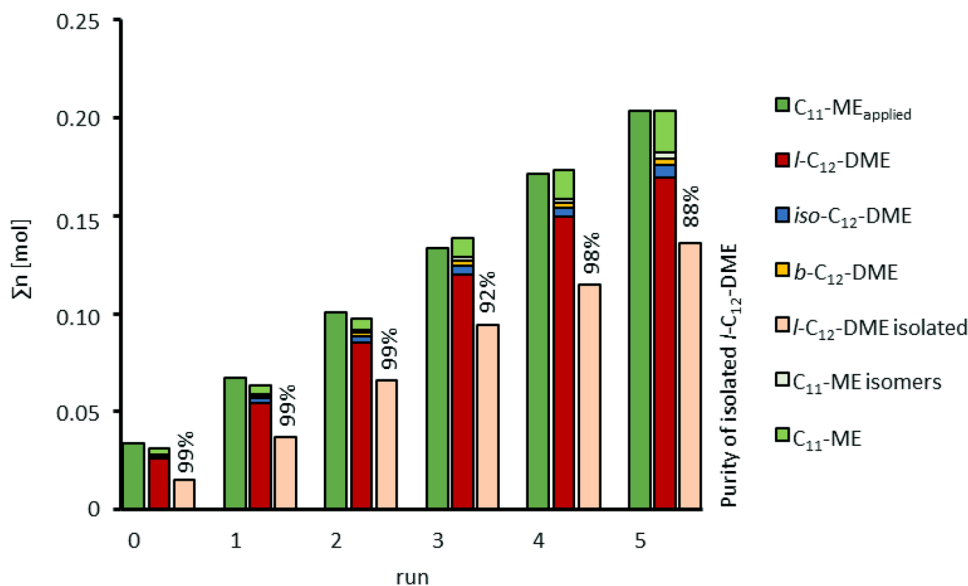


Figure 5. Selective product crystallization as catalyst recycling concept in the methoxycarbonylation of C_{11} -ME applying 1,2-DTBPMB and 1,2-DTBPMBH₂(Otf)₂ in a ratio of 1:1.

Reaction conditions: C_{11} -ME (33 mmol initially and replenished prior to each run), Pd₂(dba)₃ (0.05 mol%)/Pd:substrate 1:1000, 1,2-DTBPMB (0.875 mol%), 1,2-DTBPMBH₂(Otf)₂ (0.875 mol%), ligand: Pd₂(dba)₃ 35:1, MSA (1.75 mol%, MSA:1,2-DTBPMB 2:1, MSA: Pd 35:1), MeOH (48 g), $T = 95\text{ }^{\circ}\text{C}$, $t = 10\text{ h}$, $p(\text{CO}) = 30\text{ bar}$. Crystallization: $T_{\text{start}} = 20\text{ }^{\circ}\text{C}$; cooling rate = $0.5\text{ }^{\circ}\text{C min}^{-1}$, $T_{\text{end}} = -5\text{ }^{\circ}\text{C}$. Molar quantities are calculated via GC-FID-analysis using n-dodecane as internal standard (sampling after methoxycarbonylation and samples of isolated product are analyzed). Purity is given per run and not as average.

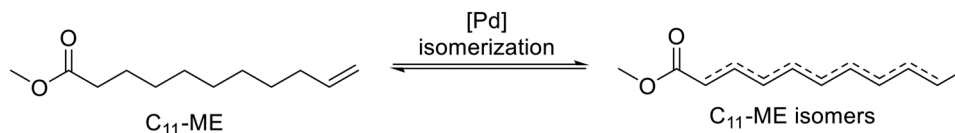


Figure 6. Pd-catalyzed double bond isomerization of C_{11} -ME.

ratio of 1:1. As aforementioned, the nonconverted substrate and side products remain in the mother liquor and are recycled to the reactor in the catalyst solution. This also includes isomers of the substrate according to the double bond isomerization shown in **Figure 6**.

On the one hand, this is beneficial, since the value product l - C_{12} -DME is purified while additional separation of those compounds is not of need. On the other hand, the occurrence of the organic side products results in increased solubility of the organic linear diester and therefore reduced isolated yield. The targeted, maximum Σ TON after six runs would be 6000, showing that the catalyst system is highly productive and our recycling study very well reproducible. Most importantly, the reaction system is tolerant against minor changes in the catalyst system, offering potential for further modifications. However, we still observed precipitation of Pd black, which indicates that first, the active catalyst is even more productive than calculated, but second, deactivation still occurs. Since the diprotonated ligand was shown to reactivate Pd⁰,^[36] our idea was to eventually improve catalyst recycling through the application of the diprotonated ligand as the sole ligand and also replenish it during catalyst recycling (**Figure 7**). Thereby, the addition of MSA is not necessary since the acid is integrated in the diprotonated ligand.

Again, similar results in terms of a Σ TON of 5300 (previously 5010 using 1,2-DTBPMB and 1,2-DTBPMBH₂(Otf)₂ in a ratio of 1:1) regarding l - C_{12} -DME, and the isolated yield of 60% are achieved. However, selectivity toward the linear product is slightly reduced. Since precipitation of Pd black is again observed after each run, significant reactivation of Pd⁰ does not occur and might need a longer time. However, Pd black is retained in the fritted crystallizer and would not be recycled into the reactor. Although the reaction system is tolerant against changes in the catalyst system, and the catalyst remains active even after five recycling runs, precipitation of Pd black indicates a rather low catalyst stability. For the implementation of an industrial process, long-term stability would be more economic. Thus, our interest was in the investigation of another, potentially more stable catalyst system for methoxycarbonylation of C_{11} -ME toward a more industrially feasible process. Therefore, we chose Xantphos that is known more robust during catalyst recycling in the methoxycarbonylation of C_{11} -ME from previous works.^[24]

In a first experiment, we simply transferred our optimized conditions to Pd/Xantphos (**Figure 8**). Thereby, reaction time was prolonged to 16 h, to ensure high conversion even with a potentially less active catalyst system.

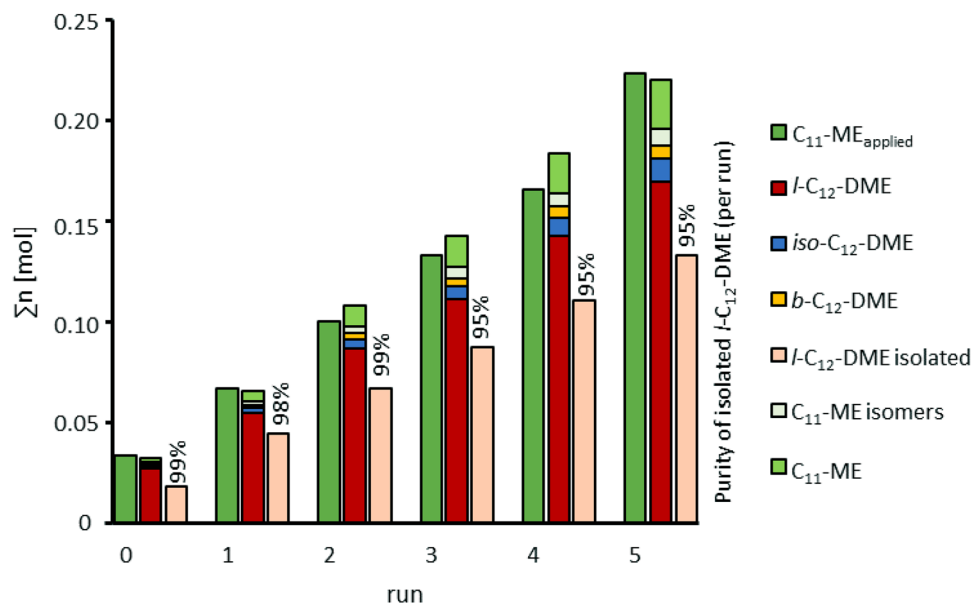


Figure 7. Selective product crystallization as catalyst recycling concept in the methoxycarbonylation of C_{11} -ME applying 1,2-DTBPMH₂(Otf)₂. Reaction conditions: C_{11} -ME (33 mmol initially and replenished prior to each run), Pd₂(dba)₃ (0.05 mol%)/Pd:substrate 1:1000, 1,2-DTBPMH₂(Otf)₂ (1.75 mol% and replenishment of 20% of initial amount prior to each recycling run), ligand: Pd₂(dba)₃ 35:1, MeOH (48 g), $T = 95\text{ }^{\circ}\text{C}$, $t = 10\text{ h}$, $p(\text{CO}) = 30\text{ bar}$. Crystallization: $T_{\text{start}} = 20\text{ }^{\circ}\text{C}$; cooling rate = $0.5\text{ }^{\circ}\text{C min}^{-1}$, $T_{\text{end}} = -5\text{ }^{\circ}\text{C}$. Molar quantities are calculated via GC-FID analysis using n-dodecane as internal standard (sampling after methoxycarbonylation and samples of isolated product are analyzed). Purity is given per run and not as average.

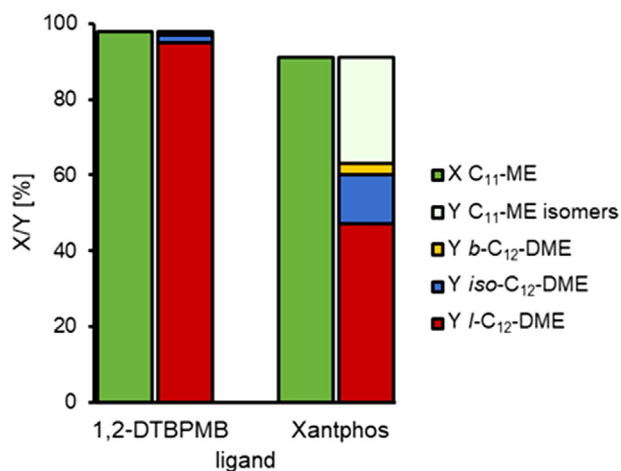


Figure 8. Comparison of 1,2-DTBPMB and Xantphos in the methoxycarbonylation of C_{11} -ME.

Reaction conditions: C_{11} -ME (33 mmol), Pd₂(dba)₃ (0.05 mol%)/Pd:substrate 1:1000, ligand (1.75 mol%), ligand: Pd₂(dba)₃ 35:1, MSA (3.75 mol%, MSA: Pd₂(dba)₃ 70:1, MSA: Pd 35:1), MeOH (48 g), $T = 95\text{ }^{\circ}\text{C}$, $t = 16\text{ h}$, $p(\text{CO}) = 30\text{ bar}$. Conversion (X) and yield (Y) are determined via GC-FID-analysis using n-dodecane as internal standard (sampling after methoxycarbonylation and samples of isolated product are analyzed).

Under our optimized reaction conditions, Xantphos is significantly less active in the methoxycarbonylation of C_{11} -ME 1, resulting in a fair yield of l - C_{12} -DME of 47%. In addition, selectivity toward the linear diester l - C_{12} -DME is significantly reduced from 30:1 to 3:1. Although the low selectivity toward l - C_{12} -DME

might be compensated through selective crystallization thereof afterward, higher catalyst productivity, here given as conversion in the methoxycarbonylation, would be more economic. Since we assume that the Pd/Xantphos system might have its optimal operating point under different conditions, we repeated the experiment based on the conditions described by Vorholt et al. for small laboratory scale.^[23] For a potential recycling using cooling crystallization, a scale-up by the factor of 10 is required (Table 1).

Interestingly, scale-up results in a much higher conversion which might be due to our reaction setup. Using a dropping funnel for the addition of the substrate with pressure compensation allows for a defined reaction start, so that potential isomerization of the substrate during heating is avoided (see Figure 9 for schematic setup and the Supporting Information for details).

As expected, selectivity toward l - C_{12} -DME is reduced to an l :(b + iso) ratio of 70:30 using Xantphos. As shown in our previous work,^[35] cooling crystallization allows for the selective separation of the linear diester from the reaction mixture in high purity, using a selective catalyst system. Thus, our aim in this work is to test the limit of this approach and combine selective cooling crystallization to compensate lowered regioselectivity with a potentially more stable catalyst system in the methoxycarbonylation.

Before, we investigated the P: Pd ratio (Figure 10) and MSA: Pd ratio (see Figure S4, Supporting Information) to eventually increase initial selectivity.

The P: Pd can be reduced to 5:1 without significant changes in selectivity or conversion. At a lower ratio, conversion is decreased to 92%. Thus, further experiments were conducted at a P: Pd ratio of 5:1. Similarly, the MSA: Pd ratio does not significantly affect catalyst productivity (see Figure S4, Supporting Information). However, MSA has an influence on catalyst

Table 1. Scale-up of methoxycarbonylation of C₁₁-ME.

	n C ₁₁ -ME [mmol]	X C ₁₁ -ME [%]	Y C ₁₁ -ME isomers [%]	Y <i>l</i> -C ₁₂ -DME [%]	Y <i>i</i> -C ₁₂ -DME [%]	Y <i>b</i> -C ₁₂ -DME [%]
Literature ^[23]	5	68 ^{a)}	a)	52		16
Scale-up ^{b)}	50	96	10	60	18	8

Reaction conditions: Pd₂(dba)₃ (0.1 mol%), Xantphos (1 mol%), MSA (20 mol%), methanol (1 mL per mmol C₁₁-ME), T = 90 °C, p(CO) = 30 bar, t = 16 h. ^{a)} Double bond isomerization was not considered in conversion; ^{b)} Conversion (X) and yield (Y) are determined by GC-analysis with n-dodecane as internal standard.

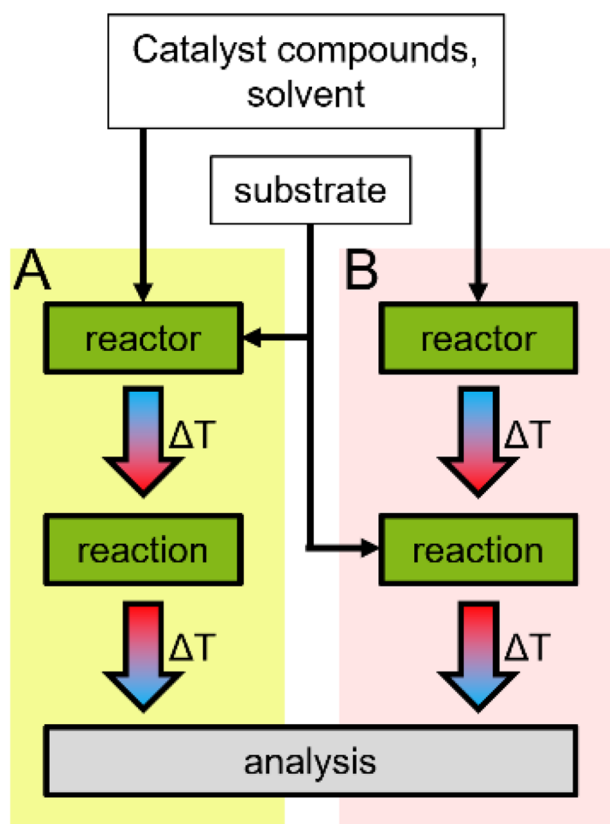


Figure 9. Schematic setup used for methoxycarbonylation of C₁₁-ME A) as described in literature^[23] and B) after our scale-up.

stability, as determined via ICP-OES of the reaction solution after the reaction (see Figure S5, Supporting Information). Thereby, the highest recovery of Pd was found at the highest MSA: Pd ratio. Interestingly, this is contrary to the results upon recovery of Pd in the Pd/1,2-DTBPMB system (Figure 3). Generally, the catalyst system of Pd/Xantphos is more tolerant for changes in MSA concentration regarding both, productivity and stability, which is also in accordance with previously described results.^[24] Hence, a ratio of 200:1 is applied for our recycling study (Figure 11) at a P: Pd ratio of 5:1. MSA was replenished twice during recycling to increase catalyst stability (see Figures S4 and S5, Supporting Information). In the same runs, reaction time was prolonged to 24 h to get information upon both, catalyst activity, which might be reduced after several recycling runs and catalyst productivity, which could then be increased even at lower catalyst activity.

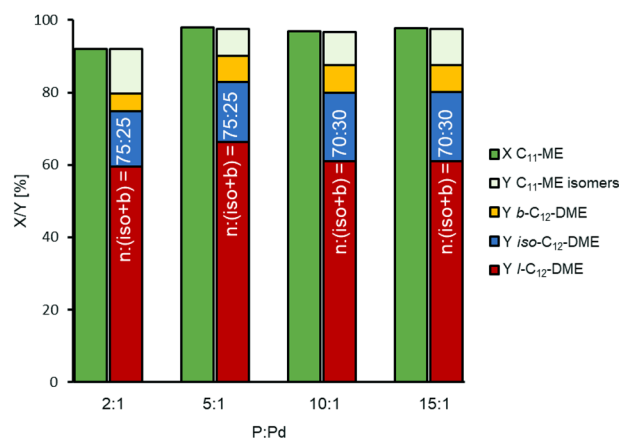


Figure 10. Effect of P: Pd ratio on catalyst productivity in the Pd/Xantphos-catalyzed methoxycarbonylation of C₁₁-ME.

Reaction conditions: C₁₁-ME (50 mmol), Pd₂(dba)₃ (0.1 mol%), Xantphos, MSA (7 mol%, MSA: Pd 35:1), methanol (40 g), T = 95 °C, p(CO) = 30 bar, t = 16 h. Conversion (X) and yield (Y) are determined by GC-analysis with n-dodecane as internal standard.

Using Xantphos as ligand, we were able to carry out nine recycling runs, and ten runs in total respectively, reaching a Σ TON of 3500 (5300 after six runs using 1,2-DTBPMB₂(OTf)₂) regarding *l*-C₁₂-DME, and a Σ TON of 4000 (5500 after six runs using 1,2-DTBPMB₂(OTf)₂) regarding C₁₂-DME (all isomers) respectively. Of course, the Σ TON in our Xantphos system is significantly lower than in our 1,2-DTBPMB system, due to the higher catalyst loading. However, focusing on the benefits of cooling crystallization, 58 g of *l*-C₁₂-DME were isolated, corresponding to an isolated yield of 52%, in an overall purity of 94% (determined from mixing the isolated products after each run). Compared to our optimized system using 1,2-DTBPMB, the isolated yield is significantly reduced, although the concentration of substrate, thus concentration of product, is increased from 12.5 to 20 wt%, due to the lowered selectivity in the methoxycarbonylation using Xantphos. Side components, such as nonconverted substrate (isomers) and *iso*- and *b*-C₁₂-DME result in a higher solubility of *l*-C₁₂-DME in the reaction mixture, so that the isolated yield is reduced. In contrast, purity of isolated *l*-C₁₂-DME is hardly influenced by reduced selectivity in the methoxycarbonylation, so that the approach of cooling crystallization is very efficient for selective product purification, even in a less selective reaction system. Interestingly, cumulated selectivity toward the linear diester in the methoxycarbonylation is increased steadily up to 80:20 after ten runs (see Table S1, Supporting Information, for selectivity after each run). Catalyst loss into the product is relatively low

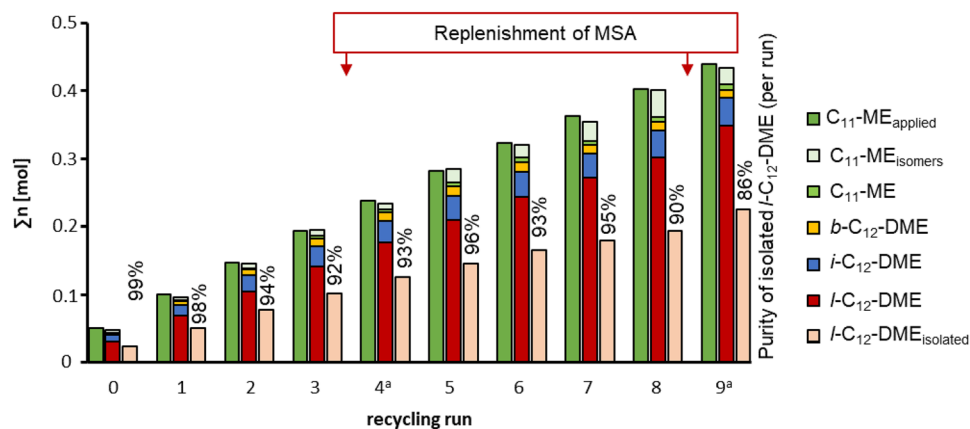


Figure 11. Selective product crystallization as catalyst recycling concept in the methoxycarbonylation of C₁₁-ME applying Xantphos as ligand. Reaction conditions: C₁₁-ME (50 mmol initially and replenished prior to each run considering sampling and thus reduced catalyst concentration), Pd₂(dba)₃ (0.1 mol%), Xantphos (0.5 mol%), MSA (MSA:Pd 200:1), methanol (40 g), T = 95 °C, p(CO) = 30 bar, t = 17 h; ^a t = 24 h. Crystallization: T_{start} = 20 °C; cooling rate = 0.5 °C min⁻¹, T_{end} = -5 °C. Molar quantities are calculated via GC-FID-analysis using n-dodecane as internal standard (sampling after methoxycarbonylation and samples of isolated product are analyzed). Purity is given per run and not as average.

with an average of 1.2% of the Pd catalyst and 2.4% of the P ligand per run (see Table S4, Supporting Information). Since the ligand is applied in excess, this discrepancy does not result in a lack of ligand. In addition, as aforementioned (Figure 9), the catalyst is still active at a lower P:Pd ratio. Finally, monitoring the reaction over time (see Figure S8, Supporting Information) in the last recycling run indicates that catalyst activity is reduced compared to the first runs. In addition, since cooling crystallization is a tool for compensation of lowered selectivity using Xantphos compared to 1,2-DTBPMB, catalyst productivity could be further increased by reducing the amount of catalyst. Thereby, we were able to increase the single TON from 450 at a catalyst loading of 0.1 mol% to a TON of 3100 at a catalyst loading of 0.01 mol%, however at a prolonged reaction time to 87 h (see Figure S7, Supporting Information). Finally, such long reaction time seems less economic, considering that using 0.1 mol% of catalyst allows for the production and purification of 58 g of *l*-C₁₂-DME 2 after 192 h (time for reaction + crystallization) in contrast to the potential production of maximum 3.2 g after 88 h (assuming that 100% of produced *l*-C₁₂-DME would be crystallized after 50 min).

3. Conclusion

The requirements toward efficient recycling of a homogeneous catalyst are a high stability and high productivity. The homogeneous Pd/1,2-DTBPMB catalyst, used for methoxycarbonylation of C₁₁-ME, is very productive but sensitive against minor changes of MSA concentration, which is measured in its stability. Thus, modification of the ligand toward its diprotonated species was carried out, resulting in a similarly high \sum TON of >5000 during catalyst recycling. Hence, cooling crystallization was proven once more highly efficient for homogeneous catalyst recycling in the methoxycarbonylation of C₁₁-ME. Pushing the approach of selective product crystallization toward its limitations, the reaction system was transferred to a different ligand. Xantphos is assumed more stable, but less selective toward the desired linear diester. However, combining the highly selective method of cooling crys-

tallization for product separation and purification with the more stable catalyst system in methoxycarbonylation allows for making use of the catalyst recycling method to compensate lower selectivity. Hence, we were able to perform a total of ten reaction runs, still maintaining a highly productive catalyst and obtaining the linear diester *l*-C₁₂-DME in a purity of 94% and an isolated yield of 52%. As the catalyst was still productive in the tenth run, it is indeed highly stable. However, for an economic process, stability and the formation of side products must both be considered, the latter resulting in the production of undesired waste. With cooling crystallization, this waste remains in the mother liquor to be recycled, which complicates setting up a continuous process. Finally, the economics of the process are a tradeoff of catalyst stability and selectivity, which must be evaluated individually and holistically. Nevertheless, this work aims at the advantages of cooling crystallization for product purification, showing high potential in the context of a less selective reaction to still obtain a pure product. Considering further increase of catalyst productivity, reduction of the initial catalyst loading at an acceptable reaction time could increase economy of the process as part of future works. In addition, the isolated yield of product might be increased through stepwise crystallization or after separation of by-products. Finally, the method of cooling crystallization could be transferred to many other reactions of renewables, even if impurities, such as by-products or nonconverted substrate are present.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

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

Keywords

1,2-DTBPMB, carbonylation, hydroesterification, methyl 10-undecenoate

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