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Single-Step Access to Long-Chain α,ω-Dicarboxylic Acids by Isomerizing Hydroxycarbonylation of Unsaturated Fatty Acids

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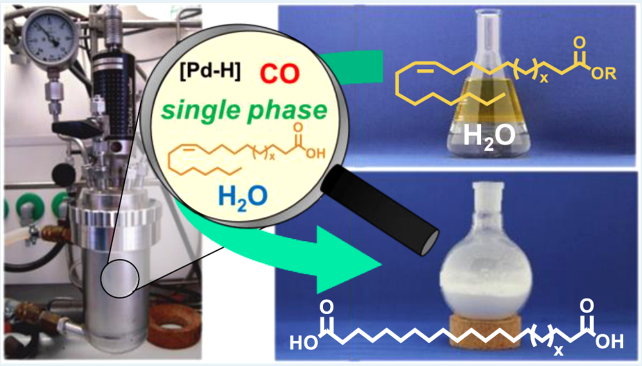
Supporting Information

ABSTRACT: Dicarboxylic acids are compounds of high value, but to date long-chain α,ω-dicarboxylic acids have been difficult to access in a direct way. Unsaturated fatty acids are ideal starting materials with their molecular structure of long methylene sequences and a carboxylate functionality, in addition to a double bond that offers itself for functionalization. Within this paper, we established a direct access to α,ω-dicarboxylic acids by combining isomerization and selective terminal carbonylation of the internal double bond with water as a nucleophile on unsaturated fatty acids. We identified the key elements of this reaction: a homogeneous reaction mixture ensuring sufficient contact between all reactants and a catalyst system allowing for activation of the Pd precursor under aqueous conditions. Experiments under pressure reactor conditions with $[(\text{dtbpx})\text{Pd}(\text{OTf})_2]$ as catalyst precursor revealed the importance of nucleophile and reactant concentrations and the addition of the diprotonated diphosphine ligand $(\text{dtbpxH}_2)(\text{OTf})_2$ to achieve turnover numbers >120. A variety of unsaturated fatty acids, including a triglyceride, were converted to valuable long-chain dicarboxylic acids with high turnover numbers and selectivities for the linear product of >90%. We unraveled the activation pathway of the Pd^{II} precursor, which proceeds via a reductive elimination step forming a Pd^0 species and oxidative addition of the diprotonated diphosphine ligand, resulting in the formation of the catalytically active Pd hydride species. Theoretical calculations identified the hydrolysis as the rate-determining step. A low nucleophile concentration in the reaction mixture in combination with this high energetic barrier limits the potential of this reaction. In conclusion, water can be utilized as a nucleophile in isomerizing functionalization reactions and gives access to long-chain dicarboxylic acids from a variety of unsaturated substrates. The activity of the catalytic system of hydroxycarbonylation ranks as one of the highest achieved for isomerizing functionalizations in combination with a high selectivity for the linear product.



KEYWORDS: *isomerizing functionalization, fatty acid functionalization, water as nucleophile, Pd-catalyzed carbonylation, Pd hydride, aqueous reaction medium*

INTRODUCTION

Fatty acids from plant and algae oils are attractive substrates with a unique molecular structure that can be used to generate higher-value chemicals.[1,2] Unsaturated fatty acids with their double bonds can be functionalized by chemical catalysis or enzymatic approaches, which yield a second functionality in addition to the carboxylic acid group that is already present in those fatty acids.[3]

Linear α,ω-dicarboxylic acids are important organic compounds. For example, one of the most important commodity dicarboxylic acids is adipic acid, which is used as a monomer for polyamide nylon-6,6 production. A typical midchain-length dicarboxylic acid, such as sebacic acid, is easily accessible from ricinoleic acid.[4] However, long-chain α,ω-dicarboxylic acids that maintain the entire sequence of methylene groups originating from the fatty acid substrates are of particular interest, but their synthesis often involves multiple steps or extensive workup.[5−7]

There are several options for functionalizing a fatty acid in an atom-efficient way by completely utilizing the feedstock and retaining their unique molecular structure with the long hydrocarbon backbone. Biotechnological approaches offer one possibility to access those valuable compounds in one step via enzymatic pathways from a variety of fatty acids,[8−11] but the potential of these approaches is limited due to complex

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downstreaming processes and the necessity of feeding costly glucose.[3] Transition-metal catalysis can generate a range of functional groups from unsaturated fatty acids: in particular, carbonyl functionalities such as aldehydes and ester groups that could be further transformed into carboxylic acid moieties. Hydroformylation, as the most prominent carbonylation reaction, can be carried out in an isomerizing fashion, in which the internal double bond of a fatty acid is converted to a terminal carbonyl group with high activities (average turnover frequency (TOF) for conversion of methyl oleate 35 h^{-1}).[12] Isomerizing hydroformylation can also be combined with an in situ reduction, forming valuable ω-hydroxy esters, even though this occurs with lower activities (average TOF for conversion of methyl oleate 2.6 h^{-1}).[13] However, isomerizing hydroformylation, also as a tandem hydroformylation−reduction approach, suffers from a low selectivity toward the desired difunctionalized product (40% toward linear aldehyde ester, 56% toward linear ω-hydroxy ester) due to the formation of thermodynamically slightly favored α,β-unsaturated esters in the isomerization step and their propensity for hydrogenation. In comparison, isomerizing alkoxycarbonylation with an alcohol as nucleophile has a slightly lower reaction rate than isomerizing hydroformylation (initial TOF 12 h^{-1} for conversion of methyl oleate) but a selectivity toward the linear diester of up to 96% can be achieved.[14−16]

A carbonylation of an olefin with water as a nucleophile can form carboxylic acids directly. Such hydroxycarbonylation reactions are well established for the generation of short-chain substrates, mostly from terminal olefins.[17−21] Concerning an envisioned isomerizing carbonylation with water as a nucleophile, however, the aforementioned related alkoxycarbonylation necessarily requires an alcohol for formation of the active species.[22,23] In addition, also with other catalysts, there are only a few examples of hydroxycarbonylation of terminal olefins longer than C_8 due to their poor solubility in water or a low solubility of the nucleophile water in the reaction medium, both resulting in a low reactivity.[18,24] To date, no isomerizing functionalization reaction has used water as a reactant or was conducted in the presence of water and the desired direct access toward linear long-chain dicarboxylic acids via chemical catalysis is missing.

We now report on a selective formation of long-chain α,ω-dicarboxylic acids in one step through isomerizing functionalization of fatty acids. Key features of this transformation are a matched solvent and catalyst system, including an activation pathway specific to water.

■ RESULTS AND DISCUSSION

Generation of Dicarboxylic Acids under Pressure Reactor Conditions. The isomerizing hydroxycarbonylation of an unsaturated fatty acid, such as oleic acid, with water as a nucleophile brings about several challenges, such as overcoming the immiscibility of fatty acids and water and achieving high reaction rates with high selectivities at the same time. Pd complexes bearing sterically demanding diphosphine ligands, such as 1,2-$(CH_2P^tBu_2)_2C_6H_4$ (dtbpx), have shown excellent activities and selectivities in other isomerizing carbonylation reactions in the past[14,15,23] and were therefore chosen for this approach of hydroxycarbonylation. To elucidate the key features of the catalytic system under practically relevant conditions, we used technical grade oleic acid as the substrate, which also contains saturated and multiunsaturated fatty acids of various chain lengths in addition to the desired monounsaturated oleic acid (93%; see the Supporting Information for details on composition). Oleic acid was then converted to 1,19-nonadecanedioic acid with water as a nucleophile, at high pressures of CO catalyzed by a Pd complex with dtbpx as diphosphine ligand.

A homogeneous reaction mixture allowing for sufficient contact between all reactants and the catalyst is crucial to achieve high activities of the Pd catalyst. The immiscibility of fatty acids and water prohibits a direct hydroxycarbonylation of oleic acid with CO and water without additional solvent. To obtain a homogeneous reaction mixture, as assessed under ambient conditions for practical reasons,[25] polar, mainly aprotic solvents having good miscibility properties with water and fatty acids were screened for isomerizing hydroxycarbonylation of oleic acid (Table 1). We chose a reaction temperature of 125 °C to overcome potential barriers and added a slight excess of trifluoromethanesulfonic acid (TfOH) and diphosphine ligand dtbpx in a 2:1 ratio, as the diprotonated diphosphine ligand $(dtbpxH_2)(OTf)_2$, to stabilize the Pd catalyst under these conditions.

Table 1. Solvent Screening for Isomerizing Hydroxycarbonylation of Oleic Acid[a]

entry	solvent	conversion[c] (%)	selectivity[c] (%)
1	ethyl acetate	2.6	72.7
2	2-methyl-THF	14.8	42.8
3	DMSO	2.9	66.9
4	diglyme	34.7	91.0
5	1,2-dimethoxyethane	42.3	89.7
6	1,4-dioxane	33.9	93.2
7	methyl ethyl ketone	41.7	85.6
8	^{t}BuOH	33.9	92.5
9	THF	31.3	91.3
10[b]	1,2-dimethoxyethane	52.7	91.2
11[b]	THF	61.0	92.6

[a] Reaction conditions unless specified otherwise: 25 μmol of $[(dtbpx)Pd(OTf)_2]$, 75 μmol of $(dtbpxH_2)(OTf)_2$, 5 mmol of technical grade oleic acid (Dakolub MB6098, 93% oleic acid content), 1 mL of H_2O, 10 mL of solvent, 20 bar of CO (initial pressure), 125 °C, 18 h. [b] 50 μmol of $[(dtbpx)Pd(OTf)_2]$, 120 μmol of $(dtbpxH_2)(OTf)_2$, 10 mmol of technical grade oleic acid. [c] Conversion and selectivity for linear products determined by gas chromatography from crude reaction mixture.

With ethyl acetate or 2-methyl-THF as solvent, the reaction mixtures were not entirely homogeneous under the chosen conditions, giving turbid suspensions upon mixing of all components. Consequently, low conversions were observed (Table 1, entries 1 and 2). By using DMSO, which gave a homogeneous reaction mixture, oleic acid was only converted to a minor extent (<3% conversion, entry 3). Since DMSO is presumably coordinating to the Pd center, active sites on the catalyst were blocked, causing a low conversion rate. Using solvents bearing oxygen functionalities that do not coordinate strongly or react in the carbonylation reaction (entries 4−9) increased conversions above 30% were observed. With THF as a solvent the best activities and selectivities toward the desired linear dicarboxylic acid under pressure reactor conditions were achieved (entry 9). THF also gave best results regarding activity and selectivity of the catalyst in experiments with higher oleic acid concentrations in comparison to 1,2-dimethoxyethane under identical conditions (entries 10 and 11). THF was also

Table 2. Variation of Temperature, Amount of Solvent, Substrate, and Nucleophile Concentration in Isomerizing Hydroxycarbonylation in Homogeneous Reaction Mixtures[a]

entry	n(OA) (mmol)	V(THF) (mL)	$V(H_2O)$ (mL)	$c(H_2O)$ (mol L^{-1})	T (°C)	conversion[b] (%)	selectivity[b] (%)	TON[c]
1	2.5	10	1	4.7	90	13.8	91.8	6.9
2	2.5	10	1	4.7	110	41.5	93.0	21
3	2.5	10	1	4.7	125	71.1	92.1	36
4	2.5	10	1	4.7	135	60.8	89.5	30
5	2.5	10	1	4.7	150	28.8	84.9	14
6	5	10	1	4.4	125	71.5	93.1	72
7	5	7	1	5.7	125	87.6	92.8	88
8	10	10	1	3.9	125	61.0	92.6	122

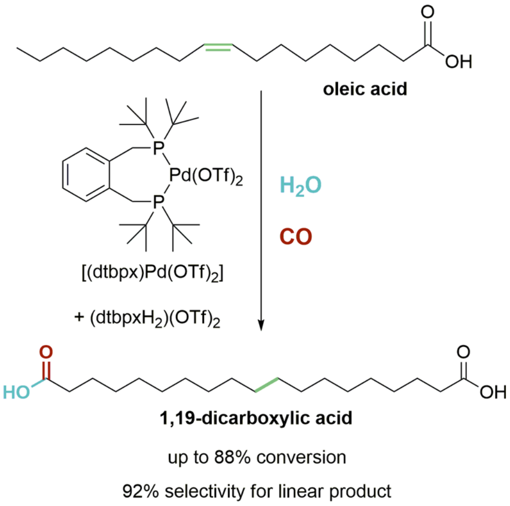
[a] Reaction conditions: 50 μmol of $[(dtbpx)Pd(OTf)_2]$, 120 μmol of $(dtbpxH_2)(OTf)_2$, technical grade oleic acid (Dakolub MB6098, 93% oleic acid content), 20 bar of CO (initial pressure), 18 h. [b] Conversion and selectivity for linear products determined by gas chromatography from the crude reaction mixture. [c] Turnover number in units of (mol of products) (mol of Pd)$^{-1}$.

the solvent of choice for the following experiments because of its volatility and easy removal from the reaction mixture as well as miscibility properties with all components, in particular the dissolution of the long-chain reaction products.

The effect of temperature, amount of solvent, substrate, and nucleophile concentration was studied, and the results are shown in Table 2.

In addition to the homogeneity of the reaction mixture, the reaction temperature also turned out to be a key factor in achieving a high turnover number (TON) in the conversion of oleic acid. Experiments under typical carbonylation conditions with $[(dtbpx)Pd(OTf)_2]$ as a catalyst precursor (90 °C, 20 bar of CO, 18 h) with a homogeneous reaction mixture containing oleic acid and water in THF surprisingly gave very low activities and a low conversion (Table 2, entry 1). Increasing the reaction temperature to 125 °C resulted in a higher TON (Table 2, entries 1−3). Between 90 and 125 °C the desired linear product is obtained with a high selectivity of around 92% (Scheme 1).

Scheme 1. Isomerizing Hydroxycarbonylation of Oleic Acid To Generate Linear, Long-Chain α,ω-Dicarboxylic Acids



At even higher reaction temperatures lower activities were observed (Table 2, entries 4 and 5). Substantial amounts of Pd black were observed for temperatures above 135 °C, suggesting catalyst decomposition at higher temperatures. At the same time, selectivity toward the desired linear product decreased slightly, as competing pathways forming alkyl-branched dicarboxylic acids, which typically have a higher energetic barrier,[15] also become energetically more feasible under those conditions, relative to the energetic barrier for the linear product.

As outlined, a homogeneous reaction mixture[25] is crucial to achieve a satisfactory conversion for this reaction. At the same time, high concentrations of the reactants are desirable to maximize the reaction rates. Increasing the amount of oleic acid and decreasing the amount of THF resulted in higher turnover numbers (Table 2, entries 6 and 7). Under these conditions, a high selectivity for the linear dicarboxylic acid and, in particular, a high substrate conversion were achieved. However, a further reduction of the amount of THF was limited by the immiscibility of the fatty acid substrate with water. Reaction mixtures with larger quantities of water showed phase separation under ambient conditions, and subsequently, conversions were significantly lower (see Table S1 in the Supporting Information). The concentration of the nucleophile is limited and greatly affects the reaction rates of the conversion. When even lower concentrations of water were applied ($c(H_2O) < 3.3$ mol L^{-1}), significant amounts of palladium black were observed, indicating catalyst instability (see Table S1). From these observations, we assume that a certain concentration of H_2O is necessary to obtain a stable catalyst and a satisfactory conversion of the substrate.

The best TON with a high selectivity toward the desired linear product was achieved with a further increase in the oleic acid concentration while the reaction mixture was kept homogeneous by adapting THF and water ratios (Table 2, entry 8). The concentration of the nucleophile H_2O is relatively low for this reaction mixture but is still in a significant excess to the oleic acid substrate.

An evaluation of the CO pressure and its influence on the activity of the catalyst revealed that the turnover numbers did not change significantly between 20 and 40 bar of CO and decreased for lower CO pressures (see Table S2 in the Supporting Information).

With an average turnover frequency (TOF) of 6.8 h^{-1} the isomerizing hydroxycarbonylation of long-chain unsaturated fatty acids ranks as one of the most active transformations in isomerizing functionalization reactions. This value is lower than a typical average TOF in Rh-catalyzed isomerizing hydroformylation (35 h^{-1} for methyl oleate),[12] but hydroxycarbonylation has a significantly higher selectivity toward the desired linear product (92% for linear dicarboxylic acid in hydroxycarbonylation vs 40% for linear aldehyde ester in hydroformylation). Isomerizing alkoxycarbonylation of methyl oleate

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with an initial TOF of 12 h^{-1} is the only isomerizing functionalization outranking hydroxycarbonylation of fatty acids regarding catalyst activity with a comparable selectivity for the linear products.[3,15] However, it is important to take into account that the concentration of the nucleophile affects these reaction rates directly. A typical nucleophile concentration, e.g. of methanol, that serves as solvent and nucleophile in alkoxycarbonylation, is five times higher in comparison to the water concentration in a solvent−water−oleic acid mixture as needed for hydroxycarbonylation, which highlights the potential of hydroxycarbonylation to functionalize unsaturated substrates with excellent catalyst activities.

Key Features of the Catalytic System under Pressure Reactor Conditions. The role of the excess of diphosphine ligand and strong, but weakly coordinating acid TfOH, also as the diprotonated diphosphine ligand $(dtbpxH_2)(OTf)_2$, was further elucidated under pressure reactor conditions. Previously optimized reaction conditions of temperature, nucleophile and substrate concentrations, solvent, CO pressure, and $[(dtbpx)Pd(OTf)_2]$ as a catalyst precursor were applied for the conversion of oleic acid (Table 3).

Table 3. Variation of Excess Ligand dtbpx and Acid TfOH in Isomerizing Hydroxycarbonylation of Oleic Acid[a]

entry	n(dtbpx) (μmol)	n(TfOH) (μmol)	conversion[b] (%)	selectivity[b] (%)	TON[c]
1	0	0	20.0	89.7	40
2	50 (as $(dtbpxH_2)(OTf)_2$)		49.1	92.6	98
3	120 (as $(dtbpxH_2)(OTf)_2$)		61.0	92.6	122
4	170 (as $(dtbpxH_2)(OTf)_2$)		64.4	92.7	129
5	0	120	7.4	92.8	15
6	0	550	2.2	93.7	4.4
7	120	0	2.1	90.9	4.2
8	550	0	<1	n.d.	n.d.

[a] Reaction conditions: 50 μmol of $[(dtbpx)Pd(OTf)_2]$, 10 mmol of oleic acid (technical grade, Dakolub MB6098, 93% oleic acid content), 10 mL of THF, 1 mL of H_2O, 20 bar of CO (initial pressure), 125 °C, 18 h. [b] Conversion and selectivity for linear products determined by gas chromatography from crude reaction mixture. [c] Turnover number in units of (mol of products) (mol of Pd). n.d. = not determined.

By a comparison of conversions and TONs of isomerizing hydroxycarbonylation of oleic acid with varying amounts of additional acid TfOH and diphosphine ligand dtbpx, in a 2:1 ratio as the diprotonated ligand $(dtbpxH_2)(OTf)_2$ (Table 3, entries 1−4), it becomes evident that the reaction rates are significantly enhanced in the presence of $(dtbpxH_2)(OTf)_2$. The addition of 1 equiv of $(dbtpxH_2)(OTf)_2$ to the precursor $[(dtbpx)Pd(OTf)_2]$ already resulted in a 2-fold increase of the conversion of oleic acid. An excess greater than 2.5 equiv in relation to the palladium precursor did not result in further substantial increases in TONs.

In contrast to this, the addition of the acid TfOH or the diphosphine dtbpx alone to the catalyst precursor $[(dtbpx)Pd(OTf)_2]$ decreased the conversion of oleic acid significantly in all experiments. In the presence of TfOH, substantial amounts of palladium black were observed after the carbonylation reaction, originating from catalyst decomposition (Table 3, entries 5 and 6). The presence of additional dtbpx to the defined diphosphine-coordinated precursor $[(dtbpx)Pd(OTf)_2]$ gave rise to even lower conversions (<5%) to the difunctionalized product (Table 3, entries 7 and 8). It can be assumed that an excess of diphosphine blocks free coordination sites on the Pd center and therefore deactivates the catalyst. We believe that a strong acid alone, such as TfOH, is not acting as a cocatalyst or promoter in this catalytic system, in contrast to what is often assumed for other carbonylation reactions.[26] However, the 2:1 addition of acid TfOH and ligand dtbpx as the protonated ligand $(dtbpxH_2)(OTf)_2$ obviously has a major beneficial impact on the activity of the Pd catalyst.

On the basis of these observations, we investigated whether the protonated ligand $(dtbpxH_2)(OTf)_2$ can form a catalytically active species in situ with a Pd precursor and how activities compare to those for a catalyst generated from a Pd precursor with separate dtbpx and TfOH (Table 4). In situ generation of the active catalyst with $Pd(OAc)_2$ or $PdCl_2$ as a metal precursor, the diphosphine ligand dtbpx, and the acid TfOH resulted in low conversions and turnover numbers for both cases, while the selectivity for the linear products remained above 90% (Table 4, entries 1 and 2). It is noteworthy that a larger excess of TfOH with these in situ systems did not have any effect on the activity of the catalyst (entry 3), in contrast to observations made with the defined precursor $[(dtbpx)Pd(OTf)_2]$ (vide supra). Remarkably, a 3-fold higher TON was observed when using $(dtbpxH_2)(OTf)_2$ instead of separate dtbpx and TfOH (Table 4, entries 4−6). These results suggest that the catalytically active species, most likely a Pd hydride, is formed very effectively in the presence of the protonated ligand.

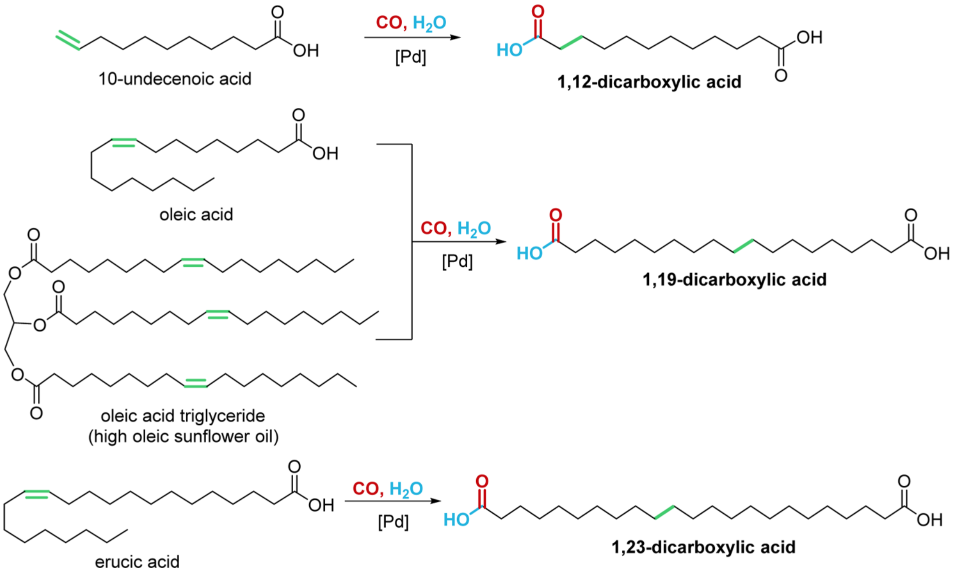
In addition to catalysis experiments with Pd^{II} precursors, $[Pd(dba)_2]$ as a Pd^0 precursor was also applied under the same reaction conditions (Table 4, entry 6). This reaction with a Pd^0

Table 4. Comparison of Catalytic Performance of in Situ Generated Catalysts in Isomerizing Hydroxycarbonylation of Oleic Acid[a]

entry	Pd precursor	n(dtbpx) (μmol)	n(TfOH) (μmol)	conversion[b] (%)	selectivity[b] (%)	TON[c]
1	$Pd(OAc)_2$	170[d]	240[e]	18.0	92.0	36
2	$PdCl_2$	170[d]	240[e]	17.3	90.6	35
3	$Pd(OAc)_2$	170[d]	670	18.1	91.2	36
4	$Pd(OAc)_2$	170 (as $(dtbpxH_2)(OTf)_2$)		53.3	91.7	107
5	$PdCl_2$	170 (as $(dtbpxH_2)(OTf)_2$)		40.7	93.1	81
6	$[Pd(dba)_2]$	170 (as $(dtbpxH_2)(OTf)_2$)		53.9	91.1	108

[a] Reaction conditions: 50 μmol of Pd precursor, 10 mmol of oleic acid (technical grade, Dakolub MB6098, 94.3% oleic acid content), 10 mL of THF, 1 mL of H_2O, 20 bar of CO (initial pressure), 125 °C, 18 h. [b] Conversion and selectivity for linear products determined by gas chromatography from crude reaction mixture. [c] Turnover numbers in units of (mol of products) $(mol\ of\ Pd)^{-1}$. [d] A 170 μmol amount of dtbpx corresponds to the amount of diphosphine ligand present in previous experiments with 50 μmol of $[(dtbpx)Pd(OTf)_2]$ and 120 μmol of $(dtbpxH_2)(OTf)_2$. [e] A 240 μmol amount of TfOH corresponds to the molar amount of protons that are present when using 120 μmol of $(dtbpxH_2)(OTf)_2$ in addition to $[(dtbpx)Pd(OTf)_2]$ (2 equiv of TfOH for generation of 120 μmol of $(dtbpxH_2)(OTf)_2$).

Scheme 2. Generation of Long-Chain Dicarboxylic Acids from Fatty Acid Derivatives via Pd-Catalyzed Isomerizing Hydroxycarbonylation



precursor showed a high turnover number that is very similar to the performance of the Pd^{II} precursor $Pd(OAc)_2$, indicating that the protonated ligand can also activate a Pd^0 precursor to generate the catalytically active Pd^{II} hydride species. This observation is important and will be discussed in more detail in the following section on the formation of the catalytically active Pd hydride species. Other Pd^0 precursors, such as $[Pd(PPh_3)_4]$ and $[Pd(P^tBu_3)_2]$, were also studied under similar conditions and showed lower turnover numbers (see Table S3 in the Supporting Information). These observations can be accounted for by the presence of coordinating phosphine ligands from the precursors, blocking coordination sites of the active catalyst. When the defined diphosphine-coordinated precursor $[(dtbpx)Pd(OTf)_2]$ is used, additional coordinating ligands or anions are not present and, therefore, this precursor gives the best catalyst performance in isomerizing hydroxycarbonylation under the given conditions. The various experiments with different Pd precursors illustrated that the protonated ligand $(dtbpxH_2)(OTf)_2$ has a crucial role in achieving high activities in hydroxycarbonylation. Pressure reactor studies alone do not allow for a conclusive picture of the mechanistic function of the protonated diphosphine ligand, and NMR studies are outlined below.

Substrate Scope of Isomerizing Hydroxycarbonylation. A selection of unsaturated substrates was further utilized in isomerizing hydroxycarbonylation to explore the scope of the reaction and to shed light on its mechanism.

To investigate if the position of the double bond within the substrate molecule has an influence on activity or selectivity of the catalyst in this reaction, 1- and 4-octene were applied to typical isomerizing hydroxycarbonylation reaction conditions (0.5 mol % of $[(dtbpx)Pd(OTf)_2]$, 1.2 mol % of $(dtbpxH_2)(OTf)_2$, 10 mL of THF, 1 mL of H_2O, 20 bar of CO, 125 °C, 18 h). Both substrates were converted with virtually identical rates (73% conversion in 3 h) and high selectivities (95% selectivity with 1- and 4-octene for linear nonanoic acid). Therefore, it can be concluded that isomerization to the thermodynamic equilibrium of all double-bond isomers is fast, and the original position of the double bond in the substrate has no influence on activity or selectivity under pressure reactor conditions for this catalytic system. These results are in unison with observations of the related isomerizing alkoxycarbonylation of internal alkenes, including different octenes, and a low energetic barrier for the isomerization, which was confirmed by DFT calculations.[15,27,28]

Various fatty acids and derivatives were used in isomerizing hydroxycarbonylation to generate valuable linear, long-chain dicarboxylic acids (Scheme 2 and Table 5).

Table 5. Substrate Scope of Isomerizing Hydroxycarbonylation for the Production of Linear Long-Chain Dicarboxylic Acids[a]

entry	substrate	conversion[b] (%)	selectivity[b] (%)
1	10-undecenoic acid	94.6	91.3
2	oleic acid	61.0	92.6
3	high oleic sunflower oil	56.9	88.8
4	erucic acid	47.4	88.1

[a] Reaction conditions: 50 μmol of $[(dtbpx)Pd(OTf)_2]$, 120 μmol of $(dtbpxH_2)(OTf)_2$, 10 mmol of fatty acid derivative (entries 1, 2, 4) or 3.33 mmol of high oleic sunflower oil (oleic acid triglyceride 93%), 10 mL of THF, 1 mL of H_2O, 20 bar of CO (initial pressure), 125 °C, 18 h. [b] Conversion and selectivity for linear products determined by gas chromatography from crude reaction mixture.

From the results in Table 5, it is evident that the conversion for different substrates from C_{10} up to C_{22} decreased with an increasing chain length of the substrate. This observation can be accounted for by our previous mechanistic studies on isomerizing alkoxycarbonylation:[15] the longer the hydrocarbon chain is, the more isomeric metal species are formed and, therefore, the concentration of the reactive terminal Pd alkyl and acyl species is lower. The rate-determining step, solvolysis, has a lower energy barrier for the terminal Pd acyl species in comparison to all other possible branched Pd acyls. With a lower concentration of the terminal species, the reaction rate decreases consequently. The selectivity also decreases to a minor extent for the conversion of the longer-chained erucic acid in comparison to oleic acid due to a larger amount of possible branched byproducts resulting from branched Pd acyl

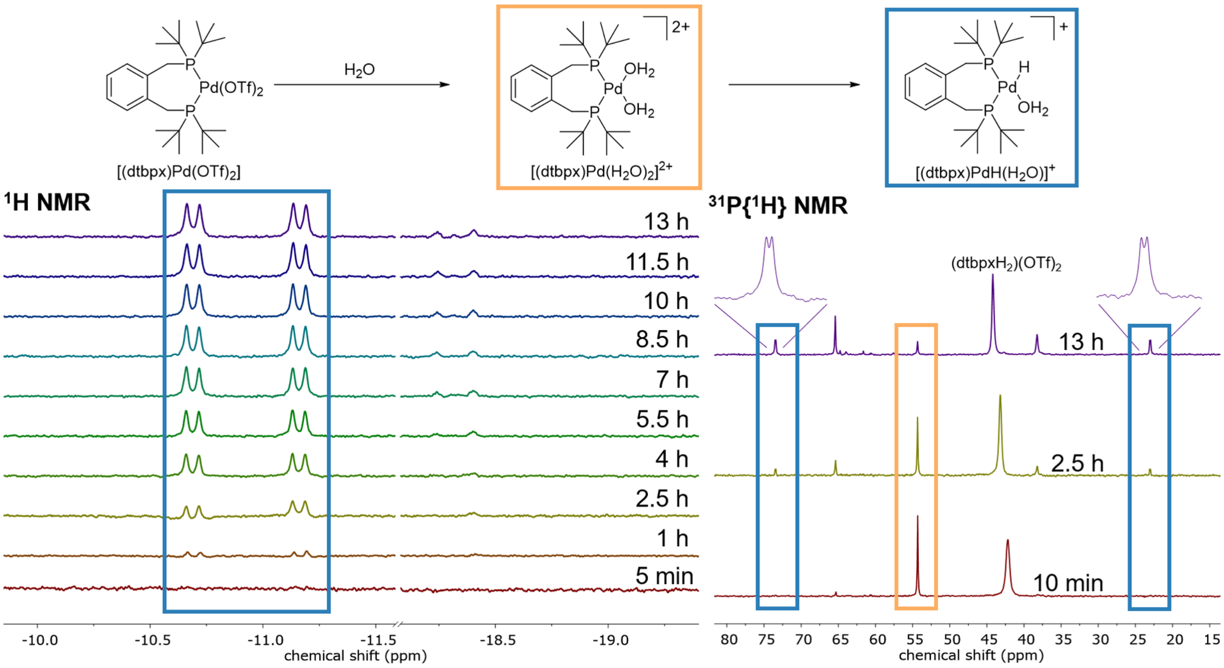


Figure 1. ^{1}H NMR (left) and ^{31}P{^{1}H} NMR spectra (right) of relevant signals monitored over time for observation of Pd hydride formation.

intermediates. Nevertheless, it is noteworthy that the C_{22} erucic acid was converted to the valuable long-chain 1,23-dicarboxylic acid with an excellent TON of 95 and a selectivity of 89% under the same conditions as for the C_{19} oleic acid.

It is remarkable that not only fatty acids themselves but also triglycerides, such as high oleic sunflower oil, can be used directly in isomerizing hydroxycarbonylation, forming the desired 1,19-dicarboxylic acid (Table 5, entry 3). Under the conditions identified for isomerizing hydroxycarbonylation (Tables 1 and 2), the ester bonds of the triglyceride are hydrolyzed, and carbonylation occurs on the terminal chain end simultaneously, generating the long-chain α,ω-dicarboxylic acids in one step. Although the reaction mixture showed phase separation upon mixing all components under ambient conditions, there is only a minor difference between conversion values of oleic acid and its triglyceride (Table 5, entry 2 vs 3). After 18 h of reaction time, the reaction mixture was completely homogeneous, and no separated phases were observed. The slightly lower conversion rate of high oleic sunflower oil could be a result of the inhomogeneous reaction mixture at the beginning of the reaction[29] and a minimally lower concentration of water over the course of the reaction, as some water is consumed by the ester hydrolysis of the triglycerides.

With these experiments, we showed that hydroxycarbonylation is not limited to short-chain or terminal alkenes but can also be utilized in combination with isomerization to generate high-value (di)carboxylic acids from a range of unsaturated substrates with a Pd catalyst and a bulky diphosphine ligand. Alkenes with terminal or internal double bonds, unsaturated fatty acids of various chain lengths, and technical grade plant oils are converted with remarkable selectivities to the desired linear (di)carboxylic acids.

Mechanistic Considerations for Isomerizing Hydroxycarbonylation. For hydroxycarbonylation reactions, it is proposed that the catalytic cycle starts with a palladium hydride species. A "hydroxy-cycle", starting from a Pd−OH species in the presence of water, is unlikely, as this would involve the formation of a highly unstable Pd−COOH species by CO insertion that rapidly undergoes elimination of CO_2 and forms a Pd hydride species.[19] However, literature is not conclusive on the formation mechanism of the active Pd hydride species, suggesting various pathways depending on the catalytic system.[19,22,23,30]

Formation of the Catalytically Active Hydride Species. To detect and observe the formation of the key compound of the catalytic cycle, the active Pd hydride complex, we transferred our catalytic system of the isomerizing hydroxycarbonylation from the pressure reactor to an NMR tube experiment. Upon dissolution of the catalyst precursor [(dtbpx)Pd(OTf)$_2$] in the presence of an excess of (dtbpxH$_2$)(OTf)$_2$ in THF and water (0.6 mL of THF, 0.15 mL of H_2O, sealed capillary filled with DMSO-d_6 as "lock stick") the diaqua complex [(dtbpx)Pd(H_2O)$_2$]$^{2+}$ was formed rapidly, as observed via ^{31}P{^{1}H} NMR spectroscopy (singlet at 54.3 ppm). From this Pd species we were able to follow the slow formation of the hydride [(dtbpx)PdH(H_2O)]$^+$ via ^{1}H and ^{31}P{^{1}H} NMR spectroscopy at room temperature (Figure 1). The ^{1}H NMR spectra reveal a characteristic doublet of doublets at −10.93 ppm ($^2J_{PH,cis}$ = 22.5 Hz, $^2J_{PH,trans}$ = 188.4 Hz) corresponding to the water-coordinated Pd hydride species [(dtbpx)PdH(H_2O)]$^+$. The corresponding signals of two inequivalent phosphorus atoms were detected via ^{31}P{^{1}H} NMR spectroscopy at 23.0 and 73.5 ppm (both $^2J_{PP}$ = 19.0 Hz). These characteristic signals match well with data reported by Clegg et al., who were also able to observe the formation of the Pd hydride [(dtbpx)PdH(H_2O)]$^+$ in a THF/water mixture.[22] Further, we observed a decline in the singlet of the initially formed [(dtbpx)Pd(H_2O)$_2$]$^{2+}$ in the ^{31}P{^{1}H} NMR spectra (Figure 1, orange boxes), while the intensities of the two doublets corresponding to [(dtbpx)PdH(H_2O)]$^+$ increase (Figure 1, blue boxes). Additional hydride signals of low intensity around −18.3 ppm in the ^{1}H NMR spectra and singlets between 60 and 65 ppm in the ^{31}P{^{1}H} NMR spectra can be assigned to reaction products from hydride formation that will be discussed later on.

Relating the hydride signals against dimethyl terephthalate as an internal standard in the ^1H NMR spectra, we concluded that a maximum of approximately 12% of the initial amount of the precursor [(dtbpx)Pd(OTf)$_2$] was transformed into the observed hydride [(dtbpx)PdH(H_2O)]$^+$ (see Figures S2 and S3 in the Supporting Information). The hydride formation is comparably slow at room temperature, and after 12 h at 300 K the maximum amount of Pd hydride species was detected with no further significant increase at longer reaction times. At elevated temperatures, the hydride formation is significantly faster. About 10% of Pd hydride was already formed within 20 min from [(dtbpx)Pd(H_2O)$_2$]$^{2+}$ and (dbtpxH$_2$)(OTf)$_2$ at 50 °C. Nevertheless, under NMR conditions, even at elevated temperatures, the Pd precursor is virtually consumed completely, but the amount of generated Pd hydride never surpassed the aforementioned maximum of hydride present in this reaction mixture (see Figure S4 in the Supporting Information).

Note that in the presence of atmospheric pressure of CO in the NMR tube no Pd hydride species were detected at room temperature with [(dtbpx)Pd(OTf)$_2$] and (dtbpxH$_2$)(OTf)$_2$ in THF/H_2O. van Leeuwen et al. have also observed this issue in their mechanistic investigations on hydroxycarbonylation of styrene with various Pd phosphine catalyst systems.[19] However, we believe that the Pd hydride [(dtbpx)PdH(L)] (L = H_2O, CO, THF) as the catalytically active species is formed in sufficient amounts in the presence of CO at higher temperatures and at higher pressures, since isomerizing hydroxycarbonylation of oleic acid was successfully run at 125 °C and 20 bar of CO in a pressure reactor (vide supra).

As previously mentioned, in addition to signals originating from the Pd hydride or starting materials, the intensity of singlets between 60 and 65 ppm in the $^{31}P\{^1H\}$ NMR spectra increased during hydride formation. These singlets can be assigned to phosphine oxides that are formed via reductive elimination from the diaqua complex [(dtbpx)Pd(H_2O)$_2$]$^{2+}$ (see the Supporting Information for comparative NMR data of phosphine oxides dtbpxO and dtbpxO$_2$, see also Figure S5), with the singlet at 65.4 ppm corresponding to the diphosphine dioxide dtbpxO$_2$. By an ESI-MS measurement of this NMR reaction mixture, the formation of dtbpxO$_2$ was confirmed (m/z calcd for $C_{24}H_{45}O_2P_2^+$ 427.29 [dtbpxO$_2$ + H]$^+$, found 427.28; m/z calcd for $C_{24}H_{44}NaO_2P_2^+$ 449.27 [dtbpxO$_2$ + Na]$^+$, found 449.26). The additional hydride signals around −18.3 ppm in the ^1H NMR spectra (Figure 1) correlate to the small singlets (61.4, 64.4 ppm) in the $^{31}P\{^1H\}$ NMR spectrum, indicating the coordination of a phosphine oxide to a Pd hydride species. The amount of these phosphine oxide Pd hydride species is usually below 2% (see Figure S2 in the Supporting Information) and, therefore, is negligible in terms of the fate of the metal.

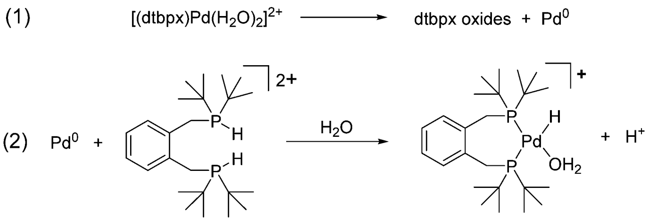
This process of a reductive elimination generating a phosphine oxide and a Pd^0 species in the presence of water was already investigated for a number of Pd systems with mono- and diphosphines as ligands[31−33] and can be expanded to our catalytic system starting from [(dtbpx)Pd(OTf)$_2$] as a precursor. NMR spectroscopy did not allow for a complete assignment of all phosphorus species in this reaction mixture (see the Supporting Information for more details). Therefore, we followed the formation of the diphosphine oxides in the absence of the protonated ligand (dtbpxH$_2$)(OTf)$_2$ in THF and water by ESI-MS (see Figure S7 in the Supporting Information).[34] At an early stage of the oxidation (after 3 h at room temperature), the diphosphine monoxide dtbpxO can be identified by ESI-MS (m/z calcd for $C_{24}H_{45}OP_2^+$ 411.29 [dtbpxO + H]$^+$, found 411.28), as well as various other dtbpx-, dtbpxO-, and dtbpxO$_2$-coordinated Pd species (see Figure S7). After a longer reaction time, ESI-MS shows only two major sets of signals at m/z 427.28 and 449.26, both corresponding to the diphosphine dioxide dtbpxO$_2$ (m/z calcd for $C_{24}H_{45}O_2P_2^+$ 427.29 [dtbpxO + H]$^+$, found 427.28; m/z calcd for $C_{24}H_{44}NaO_2P_2^+$ 449.27 [dtbpxO$_2$ + Na]$^+$, found 449.26; Figure S7). These observations confirm the oxidation of the diphosphine ligand via reductive elimination from the Pd^{II} precursor [(dtbpx)Pd(OTf)$_2$] in the presence of water. The resulting Pd^0 species, which is inevitably formed during this process, is then a crucial reactant in the next step.

While the experiment mentioned above allowed for a clear analysis of the diphosphine oxidation, we were not able to detect the hydride [(dtbpx)PdH(H_2O)]$^+$ via the characteristic signals (dd around −11 ppm) in ^1H NMR spectra in the absence of the protonated ligand (dtbpxH$_2$)(OTf)$_2$. This confirms the active role of the protonated diphosphine ligand in the hydride formation. NMR experiments with an internal standard proved that the amount of protonated ligand (dtbpxH$_2$)(OTf)$_2$ declined over time during hydride formation (see Figure S3 in the Supporting Information). Since a Pd^0 species is present from the preceding reductive elimination reaction, we assume that (dtbpxH$_2$)(OTf)$_2$ undergoes an oxidative addition, forming a Pd hydride species. The role and importance of the protonated ligand are further emphasized by pressure reactor experiments, for which a lower amount of (dtbpxH$_2$)(OTf)$_2$ resulted in significantly lower conversion of oleic acid to the 1,19-dicarboxylic acid (cf. Table 3, entries 1−4). With a lower amount of protonated ligand, less active Pd hydride is formed and consequently results in a lower conversion rate.

The feasibility of an oxidative addition of the protonated diphosphine ligand to a Pd^0 species was demonstrated by using [Pd(P^{t}Bu$_3$)$_2$] as a molecular, soluble Pd^0 precursor with (dtbpxH$_2$)(OTf)$_2$ in THF. We observed the formation of the hydride [(dtbpx)PdH(THF)]$^+$ by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy (see Figure S8 in the Supporting Information). An oxidative addition of a protonated phosphine ligand with a Pd^0 species has also been reported for other Pd catalysts.[35]

On the basis of this compiled evidence, we propose a two-step process as the major pathway for the formation of the catalytically active Pd hydride species in water. First, the diaqua complex [(dtbpx)Pd(H_2O)$_2$]$^{2+}$ undergoes reductive elimination, forming a Pd^0 species and dtbpx oxides. These Pd^0 species are then accessible for the second step, an oxidative addition of the protonated ligand, which is usually present in excess in the reaction mixtures, to generate the desired Pd hydride species [(dtbpx)PdH(H_2O)]$^+$ (Scheme 3).

Scheme 3. Proposed Pathway for Formation of the Catalytically Active Pd Hydride Species via Reductive Elimination (1) and Subsequent Oxidative Addition (2)



This two-step activation of the Pd precursor with the protonated ligand as a crucial reaction partner differs from other suggested pathways of hydride formation of a Pd precursor in carbonylation reactions. A β-H elimination pathway, which is assumed for hydride formation of a Pd precursor with a primary or secondary alcohol,[22] is not feasible for water. As already mentioned, Clegg et al. observed the formation of a hydride species in THF/H_2O as the reaction solvent and suggested an oxidation of water to generate the observed Pd hydride and O_2.[22] We did not observe any gas evolution during hydride formation, and therefore, this reaction pathway was ruled out for our catalytic system with the Pd^{II} precursor and excess protonated ligand. A different approach proposes that a Pd hydride species can be formed by a water-gas shift reaction in the presence of CO and water.[30] As elucidated, we were not able to detect any Pd hydride in the presence of CO under ambient conditions, indicating that CO does not play an essential role in activation of our Pd precursor for isomerizing hydroxycarbonylation. However, under pressure reactor conditions CO can act as another reducing agent for the Pd^{II} precursor,[19,36] generating Pd^0 that is available for the oxidative addition of the protonated ligand to form the active Pd hydride species.

This proposed pathway for the hydride formation also explains the high activities observed for the in situ approaches with Pd^0 precursors (cf. Table 4). By using a Pd^0 precursor, the entire amount of Pd is accessible for the direct oxidative addition of $(dtbpxH_2)(OTf)_2$ and reduction of the Pd^{II} precursor, which is possibly incomplete, is not required. This could eventually result in a larger amount of catalytically active Pd^{II} hydride species that participates in the catalytic cycle and the transformation of the unsaturated fatty acids to linear dicarboxylic acids. The utilization of $Pd(OAc)_2$ as a Pd^{II} precursor resulted in a high activity, comparable to results obtained with $[Pd(dba)_2]$ as precursor in isomerizing hydroxycarbonylation (TON for $Pd(OAc)_2$ 106.6 and for $[Pd(dba)_2]$ 107.8). This high activity is a result of the very effective reductive elimination and presumably complete generation of Pd^0 from $Pd(OAc)_2$, as this precursor is known to effectively undergo reductive elimination and oxidation of phosphines with water.[33]

The formation of the catalytically active Pd hydride species with a mechanism that is specific to the reaction with water is not rate-limiting in the isomerizing hydroxycarbonylation. The reaction forming the hydride is comparably slow at room temperature, but significantly faster at elevated temperatures under NMR conditions. We assume that the hydride formation occurs rapidly under pressure reactor conditions, especially at 125 °C. Pressure reactor studies showed no delay or induction period of conversion of oleic acid (see Figure S1 in the Supporting Information). This observation was further confirmed by isomerizing hydroxycarbonylation experiments of oleic acid with an additional period allowing for hydride formation in the absence of CO by stirring at room temperature or elevated temperatures before pressurizing. These experiments showed almost identical conversion in comparison to experiments without additional reaction time for hydride formation (see Table S4 in the Supporting Information). Note that, under NMR tube conditions, only a small amount of catalyst precursor was converted to the desired catalytically active Pd hydride species. Presumably, the hydride formation under pressure reactor conditions is also not quantitative, due to other competing reaction pathways, which is decisive for the catalyst performance.

Hydrolysis as the Rate-Determining Step. To gain an insight into the rate-limiting factors of hydroxycarbonylation, we investigated the crucial step of hydrolysis in isomerizing hydroxycarbonylation. This choice is based on the finding that alcoholysis is the rate-determining step in the related alkoxycarbonylation.[15,23] The decisive step of hydrolysis was examined by density functional theory (DFT) calculations, as NMR experiments alone do not allow for a comprehensive access to this important step and its overall energy profile.[37]

The dtbpx Pd^{II} acyl species $[(dtbpx)PdC(=O)(CH_2)_6COOH]^+$ has been considered as a zero point energy reference (for computational details, see the Supporting Information). The coordination of H_2O to Pd and the following insertion into the Pd−C bond leading to the formation of the linear dicarboxylic acid, plus the Pd hydride species, were calculated (Figure 2). For comparison, the energetic profile for the methanolysis of the Pd acyl species is also reported in Figure 2. For MeOH,[15] the energy profile involving a cluster of three molecules of water is favored versus a coordination of a single H_2O molecule (the difference in energetic barriers is almost 3 kcal mol^{-1}). From calculations, the energetic barrier for the hydrolysis is 30.1 kcal mol^{-1} and is 1.5 kcal mol^{-1} higher than that for the corresponding methanolysis reaction reaction (this preference for methanolysis over hydrolysis is confirmed by using different functionals; see Table S6 in the Supporting Information).

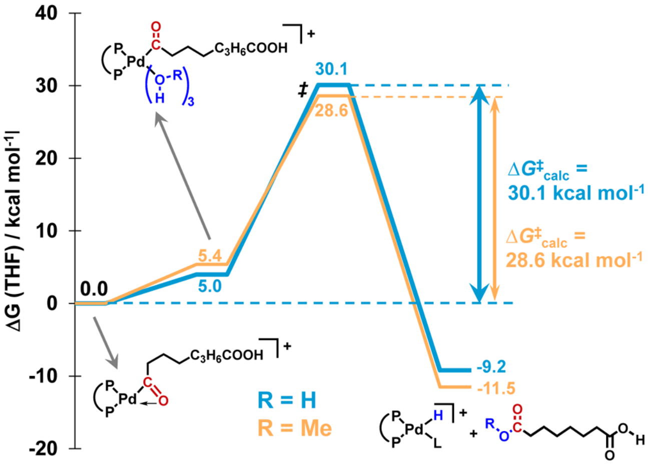


Figure 2. Energy profile (THF, in kcal mol^{-1}) of the hydrolysis (blue) and methanolysis (orange) of the linear dtbpx Pd acyl species (P^P = dtbpx).

In detail, both hydrolysis and methanolysis involve a cluster of three hydrogen-bonded molecules in which one ROH species is coordinated to the metal and another is oxygen-bonded to the acyl chain. The reductive elimination of the product occurs through a transition state in which the −OR moves from the coordinated ROH molecule to the acyl moiety and the excess of the proton is transferred to the Pd center via proton shuttle across the cluster, forming the Pd−H species (Figure 3).

A detailed analysis of the TS geometries reveals that for the hydrolysis an additional Pd−H interaction, involving the H_2O molecule bonded to the acyl moiety, occurs (see the short distance in Figure 3a) so that two different H_2O molecules interact with the Pd center in the TS. During the elimination

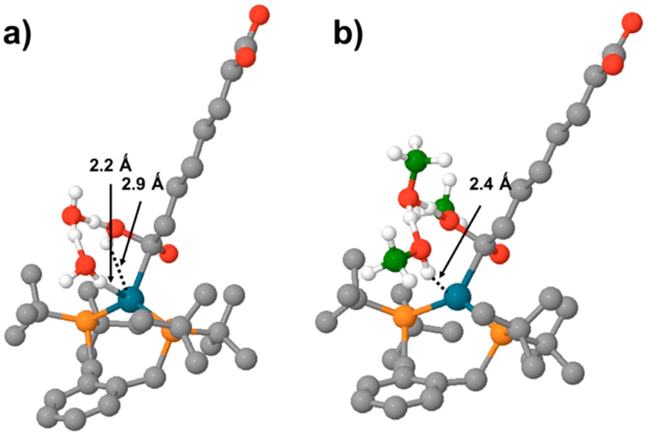


Figure 3. Transition state (TS) geometries of hydrolysis (a) and methanolysis (b). All hydrogen atoms of the Pd acyl species are omitted for clarity, and the CH_3 groups of methanol are shown in green.

process, electron density moves from the eliminating moieties to the metal; this additional Pd−H interaction makes it more difficult to transfer the proton from the H_2O-coordinated molecule to the Pd center. Vice versa, for the methanolysis, only one methanol molecule of the cluster interacts with the metal.[38]

The high energetic barrier of hydrolysis limits the rate of isomerizing hydroxycarbonylation significantly. Note that, in addition to this energetic barrier of 30 kcal mol^{-1}, the concentration of the reactive linear Pd acyl species is low in a mixture of all possible branched acyl species,[15] also limiting the reaction rates to a certain extent. Nevertheless, the calculated energetic barrier matches well with the experimental conditions identified for isomerizing hydroxycarbonylation. This energetic barrier can be overcome by a high reaction temperature of 125 °C. The reaction rates obtained with our optimized catalytic system also match well with the theoretical data (see the Supporting Information for a detailed description and comparison of isomerizing hydroxy- and methoxycarbonylation).

CONCLUSION

Linear long-chain dicarboxylic acids are valuable compounds, for example as building blocks for polyamide synthesis, but a direct access in an atom-efficient approach has not been achieved to date. Carbonylation with water as a nucleophile offers the possibility of forming such carboxylic acid functionalities from alkenes but has not been applied to internal double bonds. Unsaturated fatty acids with their internal double bonds and carboxylate functionalities are ideal starting materials for an isomerizing functionalization reaction generating long-chain α,ω-dicarboxylic acids.

Within this work, we demonstrated that water can be applied as a nucleophile in isomerizing hydroxycarbonylation and turnover numbers above 120 (for oleic acid) were achieved. This approach is suitable for various substrates with different positions of the double bond or different chain lengths and gives access to a range of long-chain α,ω-dicarboxylic acids in a single step with a selectivity for the linear products of above 90%. With water as a reactant, we unraveled a specific activation mechanism of our catalytic system consisting of a reductive elimination step from a Pd^{II} precursor forming a Pd^0 species and subsequent oxidative addition of a protonated ligand to the generated Pd^0, resulting in the catalytically active Pd hydride species. The hydride formation is presumably not quantitative, limiting the reaction rates to some extent. Further, the importance of the protonated diphosphine ligand was demonstrated by pressure reactor studies, as well as NMR experiments. Theoretical calculations showed that the rate-determining step of this isomerizing hydroxycarbonylation is the hydrolysis of the linear Pd acyl species, contributing to a significant extent to the limitation of the rates of the isomerizing hydroxycarbonylation in addition to the low concentration of the reactive terminal species. Experimentally, the limitation of this functionalization reaction is also given by a low nucleophile concentration caused by the immiscibility of fatty acids and water and the necessity of using an organic solvent. Nevertheless, the activity of the catalytic system of hydroxycarbonylation with an average TOF of 6.8 h^{-1} ranks as one of the highest achieved for isomerizing functionalization reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02622.

> Details on experimental procedures, additional pressure reactor studies, NMR experiments, ESI-MS, and computational details (PDF)

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The authors declare no competing financial interest.

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(37) A model reaction of the hydrolysis of the Pd acyl species [(dtbpx)Pd(COMe)Cl] producing acetic acid was rapid in an NMR tube experiment at room temperature (see Scheme S1 and Figure S9 in the Supporting Information).

(38) From the NPA charge analysis, the charges on Pd in the hydrolysis and methanolysis TS are −0.22 e and −0.16 e, respectively.