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Linear selective isomerization / hydroformylation of unsaturated fatty acid methyl esters – A bimetallic approach

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ABSTRACT: Herein we report about the development of an isomerization / hydroformylation tandem reaction to selectively convert fatty acid methyl esters into asymmetric *α,ω*-functionalized aldehyde esters. An orthogonal tandem catalytic system consisting of a palladium-based isomerization catalyst and a rhodium-based hydroformylation catalyst was developed using methyl 3-hexenoate as a model substrate. Using this catalyst high yields (81% at 99% conversion) and regioselectivities (*l*/*b*-ratio of 98/2) towards the desired terminal hydroformylation product are obtained in the conversion of methyl 3-hexenoate under mild conditions. Ethyl 4-decenoate was subsequently applied as a second model substrate to identify challenges associated with the longer chain length of the unsaturated ester. Finally, methyl oleate was converted using the developed catalyst system. High aldehyde yields of 74% (at 99% conversion) with an *l*/*b*-ratio of 91/9 are obtained.

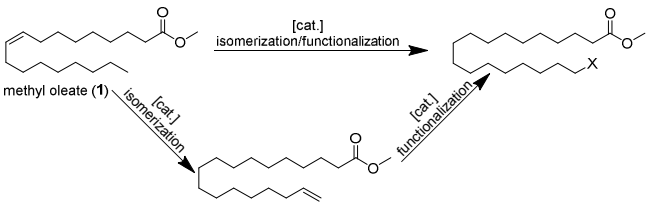
KEYWORDS hydroformylation, isomerization, tandem reactions, α,ω-functionalization, fatty acids, homogeneous catalysis

INTRODUCTION

Fatty acids and their derivatives are very interesting renewable feedstocks for the chemical industry since they naturally contain both a carboxyl function and a long carbon chain. Consequently, they are widely used as starting material in the chemical industry, e.g., in surfactant synthesis.[1]

Especially the conversion of unsaturated fatty compounds like methyl oleate (**1**) into an *α,ω*-functionalized long chained molecules (Scheme 1) is of great interest in terms of synthesizing new bio based polymer precursors.[2–5] Unfortunately, these are very challenging reaction sequences that place high demands on the applied catalysts. To reach high yields and high selectivities towards the desired products, a catalyst has to be extremely active in double-bond isomerization since the double bond has to be isomerized over many carbon atoms to the end of the chain. High chemoselectivity for the desired functionalization and high regioselectivity towards functionalization in the terminal position are also required. The transformation of unsaturated fatty compounds into *α,ω*-functionalized long chained molecules is made even more difficult because internal double bonds are thermodynamically favored over terminal ones.[6] In the case of methyl oleate, only 0.2% of all isomers contain a terminal double bond in the equilibrium mixture.[7] Mecking et al. recently published a detailed review of this topic.[8]

Of particular interest in this context are isomerization / carbonylation tandem reactions such as alkoxycarbonylations or hydroformylations. They enable the incorporation of the complete carbon chain of the fatty acid for the synthesis of potential polymer precursors.



Scheme 1: Isomerization / *ω*-functionalization of methyl oleate (1).

The isomerization / methoxycarbonylation (Scheme 2) of fatty acid methyl esters (FAMEs) first described by Cole-Hamilton et al. is a very successful example for this kind of transformation.[9] Yields of >85% and selectivities of >95% towards the linear product are achieved using a Pd/dtbx catalyst (Scheme 2). Detailed mechanistic studies have been conducted by Mecking et al.[7,10] and Köckritz et al.[11] Recently, successful approaches to recycle the Pd/dtbx catalyst using ionic liquids and thermomorphic solvent systems were also reported by Riisager et al.[12] and our group.[13,14] The conversion of FAMEs via alkoxycarbonylation leads directly to symmetric *α,ω*-functionalized diesters with potential applications as AA-type monomers.

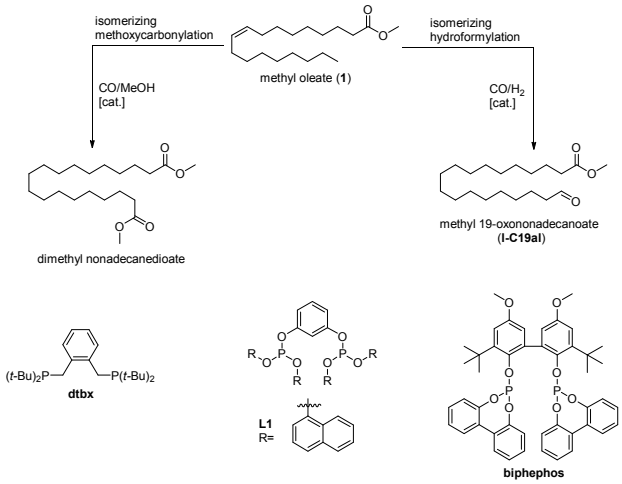
For the selective synthesis of valuable asymmetric *α,ω*-functionalized molecules, which are potential AB-type monomers, via isomerizing alkoxycarbonylation at a reasonable reaction time and with high selectivities, FAMEs have to be derivatized prior reaction (e.g. to amides).[15,16]

Isomerizing hydroformylation provides a more straightforward way of synthesizing asymmetric α,ω-functionalized molecules from FAMEs (Scheme 2). The isomerizing hydroformylation is well described for simple internal olefins and short chained unsaturated esters such as methyl 3-pentenoate.[17,18] Unfortunately, all catalysts applied in the isomerizing hydroformylation of FAMEs lead to low yields, chemo- and/or regioselectivities.

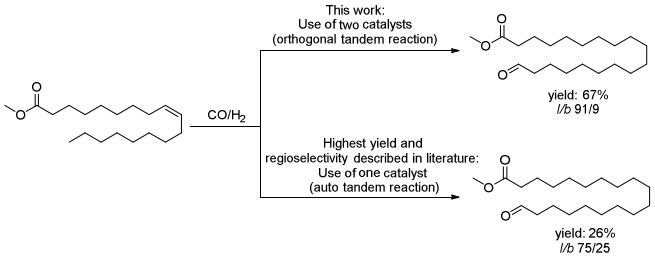
Nozaki *et al.* described the synthesis of C19-alcohols from methyl oleate (**1**) via an isomerization / hydroformylation / hydrogenation tandem reaction. The resulting aldehydes from the rhodium catalyzed hydroformylation are directly converted into corresponding alcohols by a second ruthenium catalyst. The yield of the linear alcohol is 53% with a *l*/*b*-ratio of 82/18.[19] Direct synthesis of alcohols may either be desired or not, since they already are an AB-type monomer. On the other hand, the aldehyde, as the more versatile intermediate, can be easily converted into different products (e.g., alcohols, amines, carboxylic acids).

If the aldehyde itself is targeted, yields of the linear product described in the literature regarding the isomerizing hydroformylation of methyl oleate (**1**) are even lower. A yield of 26% of the linear aldehyde can be achieved by applying a Rh/biphephos (Scheme 2) catalyst complex. The yield is slightly higher (34%) using ethyl linoleate as substrate. These are the highest yields yet reported in the literature. The ratio of linear to branched (*l*/*b*) aldehydes is about 75/25 in both reactions, which is unusually low for a Rh/biphephos catalyst.[20] The application of ligand **L1** (Scheme 2) leads to similar *l*/*b*-ratios. The yield of the desired linear product cannot be improved with this catalyst either.[21] The main problems this kind of transformation presents are that the hydrogenation of the starting material and the formation of branched aldehydes lead to low chemo- and regioselectivities if the known catalysts are applied.

Consequently, developing a new catalytic system that catalyzes the double bond isomerization from the 9 position to the carbon chains end and the linear selective hydroformylation in an efficient manner is of high interest.



Scheme 2: Isomerizing hydroformylation and methoxycarbonylation.



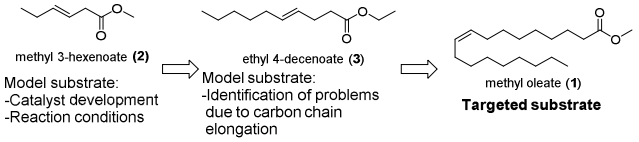
Scheme 3. Isomerizing hydroformylation of methyl oleate: This work compared with literature.

In order to overcome the limitations mentioned above, we decided to develop an orthogonal tandem reaction using two different catalysts: one catalyst for the isomerization and one catalyst for the linear selective hydroformylation of the terminal double bond. This strategy allows the reaction to proceed at mild reaction conditions, enabling the highest yields and the highest regioselectivity towards the linear aldehyde in the hydroformylation of methyl oleate (**1**) described in the literature today (Scheme 3).

RESULTS AND DISCUSSIONS

In order to identify a suitable orthogonal catalyst system as well as suitable reaction conditions, we started our investigation of isomerizing hydroformylation using methyl 3-hexenoate (**2**, Scheme 4) as a model substrate. Substrate **2** has an internal double bond and an ester moiety such as the targeted substrate methyl oleate (**1**). In principle, the same qualitative problems as in the conversion of **1** occur. The model substrate 3-methyl hexenoate with its shorter carbon chain provides crucial analytical advantages since isomers can be separated and quantified via gas chromatography.

In order to identify problems that occur in connection with the elongation of the substrates carbon chain, we decided to apply the developed catalyst systems and reaction conditions to ethyl 4-decenoate (**3**, Scheme 4) as a second model substrate, before optimizing the conditions for the isomerizing hydroformylation of methyl oleate. Scheme 4 summarizes the approach for the development of the tandem reaction.



Scheme 4: Approach for development of the isomerizing hydroformylation of FAMEs.

Catalyst development. To develop a new orthogonal tandem catalytic system for the isomerization / hydroformylation tandem reaction, we determined several selection criteria for both the hydroformylation and the isomerization catalyst. The hydroformylation catalyst needs to be very selective for functionalization in the terminal position. The activity in double bond hydrogenation needs to be as low as possible. We decided to use a Rh/biphephos catalyst, which is well known for linear selective hydroformylation and also provides the highest yields of the linear aldehyde in the hydroformylation of

methyl oleate described in the literature.[20] This catalyst also has some activity in double bond isomerization that is helpful in view of the tandem reaction.

The isomerization catalyst, on the other hand, has to be highly active in double bond isomerization in a synthesis gas atmosphere. Activity in hydrogenation and (non-selective) hydroformylation are highly undesirable. In order to find a suitable isomerization catalyst, we investigated several transition metal catalyst precursors based on Pd, Rh, Ru, Ir, Pt Co and Ni in the isomerization of methyl 3-hexenoate (**2**) under hydroformylation conditions (15 bar CO/H_2, 90 °C, most promising results are shown in Table 1, all tested precursors can be found in Table S1 and S2, supporting information). The most promising candidate was the palladium-dimer **C1** (Table 1, Entry 1.2; Scheme 6). This catalyst precursor was first synthesized by Vilar et al.[22] and described by Gooßen et al. as very effective in double bond isomerization of long chained olefins and oleocompounds in their work regarding the isomerizing metathesis tandem reaction.[23–25]

Table 1: Isomerization catalyst screening

Entry	Catalyst	High isomerization rate	No hydroformylation	No Hydrogenation
1.1	$Pd(t\text{-}Bu_3P)_2$	•	✓	✓
1.2	C1	✓	✓	✓
1.3	$PdCl_2(PPh_3)_2$	•	✓	✓
1.4	$Rh_2(OAc)_2$	✓	•	•
1.5	Shvo's catalyst	✓	✓	•

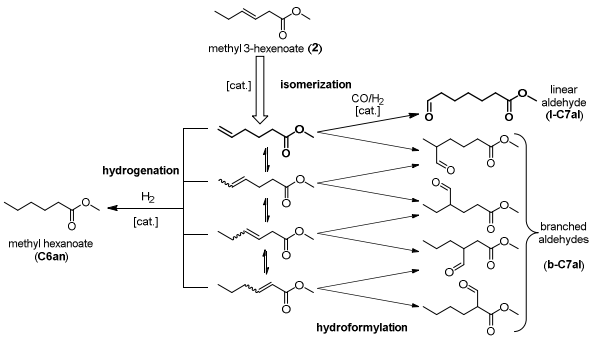
Conditions: 2.1 g toluene, 3.5 mmol **2**, 1 mol% metal, 15 bar synthesis gas (absolute pressure; CO/H_2 = 1/1/), 16 h, 90 °C, batch reaction in 20 mL autoclave, stirrer speed 500 rpm.

✓= Meets criterion fully, •= Meets criterion in an acceptable manner; ×= does not meet criterion

Isomerization, hydroformylation and hydrogenation are detected by GC-FID.

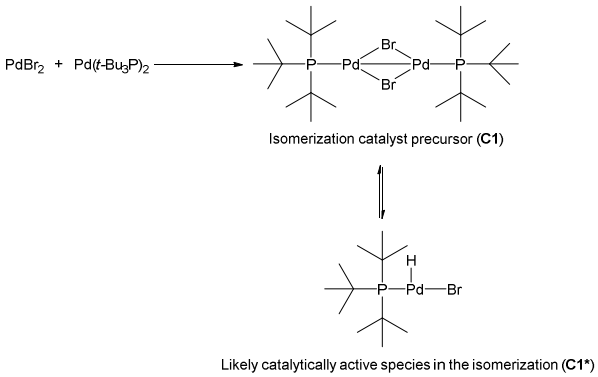
We began developing an orthogonal tandem catalytic system consisting of Rh/biphephos as the hydroformylation catalyst and **C1** as the isomerization catalyst in the isomerizing hydroformylation of **2**. Scheme 5 shows the reaction network of this reaction. The desired linear aldehyde (**l-C7al**) can only be formed from the isomer containing the terminal double bond. Branched aldehydes (**b-C7al**) and the hydrogenated substrate (**C6an**) can be formed from any isomer of **2**. Especially the *α,β*-unsaturated isomer of **2** is very prone for hydrogenation.[20]

If the Rh/biphephos catalyst was applied without the addition of **C1** (Table 2, Entry 2.1), the yield of the linear aldehyde (**l-C7al**) is 59% under the given conditions. The *l*/*b*-ratio is 81/19, which is relatively low for this catalyst compared to the results obtained if the internal olefins are converted (>90/10) and the yield of the hydrogenated substrate (**C6an**) is 15%.



Scheme 5: Reaction network of the isomerizing hydroformylation of 2.

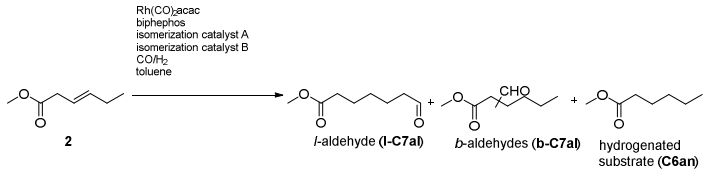
When 0.5 mol% of **C1** was added, much better results were obtained (Entry 2.2). The yield of **l-C7al** increased to 68% with a high *l*/*b*-ratio of 95/5. Also, substrate hydrogenation was slightly suppressed with 10% of **C6an** obtained. The **C1** amount added had strong influence on the outcome of the reaction (Entries 2.2 – 2.4). When the amount of **C1** was decreased to 0.25 mol%, yield of **l-C7al** was comparable (65%), but the *l*/*b*-ratio decreased drastically to 82/18 while the yield of hydrogenated **C6an** was 17%. On the other hand, when 1 mol% **C1** was added, the *l*/*b*-ratio was even higher (98/2) but the activity of the Rh/biphephos catalyst was inhibited and only 45% of **l-C7al** were formed.



Scheme 6: Synthesis of C1 and likely catalytically active species according to Gooßen et al.[26,27]

However, in light of these first promising results, we decided to study this orthogonal catalyst system in greater detail. We were first interested in the role of the Pd-dimer **C1**. According to Gooßen et al. this compound can be synthesized via comproportionation of $PdBr_2$ and $Pd(t\text{-}Bu_3P)_2$ (Scheme 6).[26] We wondered if precursor **C1** is necessary to form the catalytically active isomerization species or if it could be formed merely by adding $PdBr_2$ and $Pd(t\text{-}Bu_3P)_2$ to the reaction mixture under the given conditions. The latter would be advantageous since additional effort and costs would be avoided if the synthesis of **C1** is not required. A comparison of the results of the reaction using **C1** as isomerization catalyst precursor (Entry 2.2) with the use of $PdBr_2$ and $Pd(t\text{-}Bu_3P)_2$ (Entry 2.5) showed that the yield of the linear aldehyde **l-C7al** was slightly higher (73% vs 68%) when the active isomerization catalyst was formed directly from

Table 2: Catalyst development for the isomerizing hydroformylation of methyl 3-hexenoate (2).



Entry	Isomerization catalyst A	Isomerization catalyst B	Conversion[a] [%]	*l*-aldehyde (l-C7al) [%]	*b*-aldehyde (b-C7al) [%]	Hydrogenated substrate (C6an) [%]	*l*/*b*-ratio
2.1	-	-	87	59	13	15	81/19
2.2	0.5 mol% C1	-	81	68	3	10	95/5
2.3	0.25 mol% C1	-	96	65	14	17	82/18
2.4	1 mol% C1	-	54	45	1	8	98/2
2.5	0.5 mol% $PdBr_2$	0.5 mol% $Pd(t\text{-}Bu_3P)_2$	98	73	10	15	88/12
2.6	-	1 mol% $Pd(t\text{-}Bu_3P)_2$	68	49	9	10	84/16
2.7	0.5 mol% $PdCl_2$	0.5 mol% $Pd(t\text{-}Bu_3P)_2$	94	60	13	21	82/18
2.8	0.5 mol% PdI_2	0.5 mol% $Pd(t\text{-}Bu_3P)_2$	>99	81	2	17	98/2
2.9	1 mol% PdI_2	-	<1	-	-	-	-
2.10	1 mol% LiI	0.5 mol% $Pd(t\text{-}Bu_3P)_2$	15	12	<1	2	97/3
2.11	1 mol% LiI	1 mol% $Pd(t\text{-}Bu_3P)_2$	>99	78	2	19	98/2

Conditions: 2.1 g toluene, 3.5 mmol **2**, 0.4 mol% $Rh(CO)_2acac$, 1.6 mol% biphephos, 15 bar synthesis gas (absolute pressure, CO/H_2 = 1/1/), 16 h, 90 °C, batch reaction in 20 mL autoclave, stirrer speed 500 rpm. Conversion yields and *l*/*b*-ratios were determined by GC-FID.

[a] Double bond isomerization not considered in the conversion

$PdBr_2$ and $Pd(t\text{-}Bu_3P)_2$, but selectivity was slightly lower (*l*/*b*: 88/12 vs 95/5; yield **C6an** 15% vs. 10%).In principle, both precursors caused similar results in the tandem reaction, which led us to the assumption that the catalytically active isomerization species is the same in both cases. DFT studies made by Gooßen et al. in their investigations regarding the isomerization of allylic esters suggest that the catalytically active isomerization species is **C1***, formed from precursor **C1** (Scheme 6).[27] We assume this could also be the active isomerization catalyst in this case.

In order to get more information about the isomerization catalyst we conducted an experiment in which only $Pd(t\text{-}Bu_3P)_2$ was added as a precursor (Entry 2.6). The results (yield of **l-C7al** 49%, *l*/*b* = 84/16) obtained were more or less comparable with the reaction without introducing any isomerization catalyst (Entry 1.1), although the activity in hydroformylation and hydrogenation was slightly lower. We also screened the $Pd(t\text{-}Bu_3P)_2$ precursor in the isomerization of **2** without Rh/biphephos and only relatively small amounts of isomers were formed (Entry 1.1, Table 1).

We further investigated how the nature of the halide influences the tandem reaction (Entries 2.5, 2.7, 2.8). It turned out that the catalytic activity as well as the selectivity towards desired **l-C7al** increases strongly from chloride to iodide. When $PdCl_2/Pd(t\text{-}Bu_3P)_2$ was used as precursor (Entry 2.7), the yield of **l-C7al** was 60% and the *l*/*b*-ratio was 82/18, which again is quite similar to the results obtained without an additional isomerization catalyst (Entry 2.1). In contrast, by using $PdI_2/Pd(t\text{-}Bu_3P)_2$, a very high yield of **l-C7al** (81%) and an excellent *l*/*b*-ratio of 98/2 were obtained. One possible explanation for this effect is that the nature of the halide influences the formation of the catalytically active, three-coordinated Pd-isomerization species from a four-coordinated, halide-bridged dimeric resting state of the catalyst. Also a direct influence of the halide on isomerization activity of the catalytically active species cannot be excluded at this point.

However, when PdI_2 was used as precursor without $Pd(t\text{-}Bu_3P)_2$ no hydroformylation or hydrogenation was observed and only traces of isomers were formed (Entry 2.9). We assume that the iodide coordinates to the rhodium

complex in the absence of palladium leading to a complete deactivation of the rhodium catalyst.

Investigations on the halide source (use of LiI instead of PdI_2) showed that the cations nature does not influence the outcome of the tandem reaction (comparing Entries 2.8 and 2.11) but, as mentioned above, the amount of Palladium (and therefore the ratio of Pd/I^-) is crucial (comparing Entries 2.8, 2.10 and 2.11) to prevent catalyst deactivation. A Pd/I^--ratio of 1/1 led to excellent yields of **l-C7al** (~80%) and *l*/*b*-ratios (98/2) whereas an excess of iodide led to catalyst deactivation. These results also show that the oxidation state of the Pd precursor is not crucial and both the Pd(0) and the Pd(II) are converted into the active isomerization catalyst under the given conditions.

We also were interested in the distribution of the isomeric unsaturated C6-esters in the equilibrium and the distribution of the branched C7-aldehydes (**b-C7al**) (Table 3).

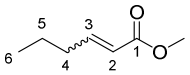
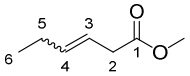
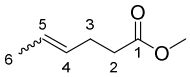
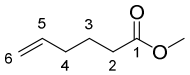
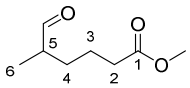
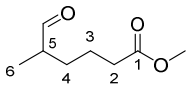
Studies of Mecking et al. regarding the isomerization of methyl 5-hexenoate showed that the *α,ß*-unsaturated isomers are the most abundant ones in the thermodynamic equilibrium (54.4% at room temperature). The equilibrium mixture contains only 0.9% of the terminal unsaturated isomers.[7] Consequently, high yield and high selectivity towards the desired linear aldehyde can only be achieved if mainly terminal unsaturated isomers are hydroformylated and therefore are selectively removed from the equilibrium. These isomers can then be regenerated by isomerization of the internal unsaturated isomers.

The distribution of the branched aldehydes formed if Rh/biphephos is applied as the only catalyst (Table 3) shows that in principle also internal double bonds can be hydroformylated under given conditions, if they coordinate to the Rh-center. 67% of all branched aldehydes are formed exclusively by hydroformylation of an internal double bond. Only 33% of the branched aldehydes contain the formyl group in position 5 of the carbon chain. This aldehyde can either be formed by hydroformylation of the terminal unsaturated C6-ester or from the unsaturated C6-ester with the double bond in position 4.

In contrast, application of the orthogonal Rh/Pd-catalyst strongly shifts this distribution towards formation of the branched aldehyde with the formyl group in position 5 (63% of all branched aldehydes; Table 3). One possible explanation for this observation is that the coordination of the terminal unsaturated substrate to the Rh/biphephos complex, which is supposed to be the rate determining step in the hydroformylation using this catalyst[28], is strongly favored over coordination of isomers with an internal double bond. If the terminal unsaturated isomers are generated by an additional isomerization catalyst, mainly these isomers will coordinate to the Rh-complex and undergo hydroformylation. This leads to an very high *l*/*b*-ratio (98/2).

After investigating the reaction parameters temperature, synthesis gas pressure and synthesis gas composition (Figure S1 –S3) and slightly adjusting (100 °C and 10 bar) the reaction conditions, we also studied the kinetics of the reaction to better understand the interplay between

Table 3: Double bond isomer distribution of 2 in the equilibrium and distribution of branched aldehydes after reaction.

Equilibrium distribution of double bond isomers (at room temperature) [7]	Distribution of branched aldehydes using only Rh/biphephos catalyst	Distribution of branched aldehydes using orthogonal Rh/Pd catalyst [a]
 54.4%		
 9.1%	**Branched aldehydes exclusively formed from internal double bonds: 67%**	**Branched aldehydes exclusively formed from internal double bonds: 37%**
 35.6%		
 0.9%	 33%	 63%

Reaction conditions: Conditions: 2.1 g toluene, 3.5 mmol **2**, 0.4 mol% $Rh(CO)_2acac$, 1.6 mol% biphephos, 15 bar synthesis gas (absolute pressure, CO/H_2 = 1/1/), 16 h, 90 °C, batch reaction in 20 mL autoclave, stirrer speed 500 rpm. Distribution of aldehyde isomers was determined by GC-FID. Identification of the formyl groups position was done by GC-MSD.

[a] Addition of 0.5 mol% PdI_2 and 0.5 mol% Pd(*t*-$bu_3P)_2$

both catalysts. Therefore, experiments with the orthogonal tandem catalytic system consisting of $Rh/biphephos/PdI_2/Pd(t\text{-}Bu_3P)_2$ (Figure 1a) were compared with experiments using only the Rh/biphephos catalyst at different temperatures (Figures 1b – 1c).

When the orthogonal catalyst was used (Figure 1a), isomerization of methyl 3-hexenoate (**2**) was extremely fast.

After ten minutes the mixture contained only 16% of the starting material and 74% isomers. At this point the isomers seem to be in equilibrium since the concentrations of 2 and its isomers decreased at the same rate. The formation of the linear aldehyde also started instantly (9% after 10 minutes).

During the first four hours, remarkably, no formation of branched aldehydes was observed. Consequently, only isomers containing a terminal double bond were consumed via hydroformylation and regenerated from the remaining isomers via isomerization. Hydrogenated substrate was also detected from the start of the reaction (1% after 0.5 h). Based on the results described in previous studies[20], it can be assumed that mainly the *α,β*–unsaturated isomer is hydrogenated. When only Rh/biphephos (Figure 1b) was applied as a catalyst at 90 °C, the isomerization rate drastically decreased. The formation of the targeted linear aldehyde **l-C7al** was slower (3% after 0.5 h) and also the formation of

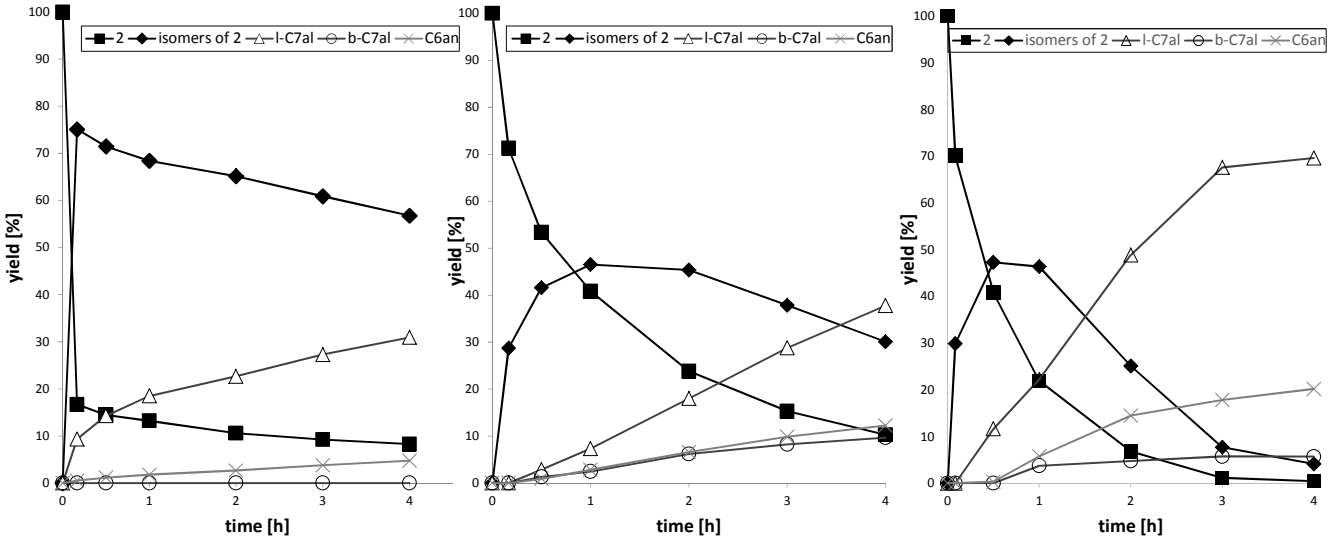


Figure 1a. Rh/biphephos/PdI_2/Pd(*t*-$Bu_3P)_2$ at 100 °C

Figure 1b. Rh/biphephos at 90 °C

Figure 1c. Rh/biphephos at 100 °C

Figure 1. Reaction kinetics of the isomerizing hydroformylation of **2.**

Figure 1a. Conditions: 48 g toluene, 70 mmol **2**, 0.4 mol% $Rh(CO)_2$acac, 1.6 mol% biphephos, 0.5 mol% PdI_2, 0.5 mol Pd(*t*-$Bu_3P)_2$ 10 bar synthesis gas (absolute pressure, CO/H_2 = 1/1/), 100 °C, batch reaction in 300 mL autoclave, stirrer speed 1000 rpm. Yields were determined by GC-FID.

Figure 1b. Conditions: 48 g toluene, 70 mmol **2**, 0.4 mol% $Rh(CO)_2$acac, 1.6 mol% biphephos, 15 bar synthesis gas (absolute pressure, CO/H_2 = 1/1/), 90 °C, batch reaction in 300 mL autoclave, stirrer speed 1000 rpm. Yields were determined by GC-FID.

Figure 1c. Conditions: 48 g toluene, 70 mmol **2**, 0.4 mol% $Rh(CO)_2$acac, 1.6 mol% biphephos, 10 bar synthesis gas (absolute pressure, CO/H_2 = 1/1/), 100 °C, batch reaction in 300 mL autoclave, stirrer speed 1000 rpm. Yields were determined by GC-FID.

undesired branched aldehydes was detected from the start of the reaction (1% after 0.5 h). Undesired hydrogenation of the substrate was more than two times faster (7% after 2 h instead of 3%) compared to the application of the orthogonal catalyst.

When the temperature was increased to 100 °C (Figure 1c), the reaction rates of all partial reactions increased as well. After two hours, aldehyde yield of 52% (*l*/*b*=90/10) and 14% of the hydrogenated substrate **C6an** were obtained.

The selectivity towards the linear aldehyde in the hydroformylation also increased with temperature. Compared to the orthogonal catalyst system, the isomerization of **2** was still much slower, though the hydroformylation (branched) and hydrogenation reaction rates were higher.

The use of the orthogonal catalyst inhibits the most important side reactions (hydrogenation and formation of branched aldehydes). The results show that selectivity towards the linear hydroformylation product correlates with the isomerization rate. As outlined above, this could be traced back to a higher coordination affinity of the terminal unsaturated substrates to the Rh/biphephos complex. If an additional isomerization catalyst is present, the "supply" of the terminal unsaturated isomers via isomerization of internal unsaturated ones is very fast, resulting in a higher *l*/*b*-ratio in the hydroformylation. This could also explain the higher chemoselectivity when the orthogonal tandem catalyst is applied, especially considering that the *α,β*-unsaturated isomer is very prone to hydrogenation.[20]

However, interactions between the transition metals and their ligands cannot be excluded at this point. For example, as shown in Table 2 (Entry 2.9 and Entry 2.10), catalytic activity is strongly inhibited if more iodide than palladium is present in the reaction mixture. This demonstrates that components of the isomerization catalyst precursor may potentially interact with the rhodium catalyst.

After successfully developing a promising orthogonal tandem catalytic system, the next step was to apply this system in the isomerizing hydroformylation of ethyl 4-deceneoate (**3**) as a second model substrate bearing a longer carbon chain.

Isomerizing hydroformylation of ethyl 4-decenoate (3). In order to identify limitations that occur when using a long chained unsaturated ester as a substrate, we tested the catalyst system in the isomerizing hydroformylation of ethyl 4-decenoate (**3**) (Figure 2). The results show that reaction rates for hydroformylation and hydrogenation were slower compared to the conversion of **2**. Aldehyde formation (1% **l-C11al**) was observed after two hours. The hydrogenation of the starting material was observed after four hours (1% yield of **C10an).** This was the case because it took more time to reach the equilibrium of the double bond isomers (Figure S4). Ratios of the isomers were unchanged after two hours. Afterwards, the reaction proceeded similar to the isomerizing hydroformylation of **2**, albeit more slowly due to the lower equilibrium concentration of the terminal unsaturated ester. The *l*/*b*-ratio of the resulting aldehydes was also slightly lower (95/5). As

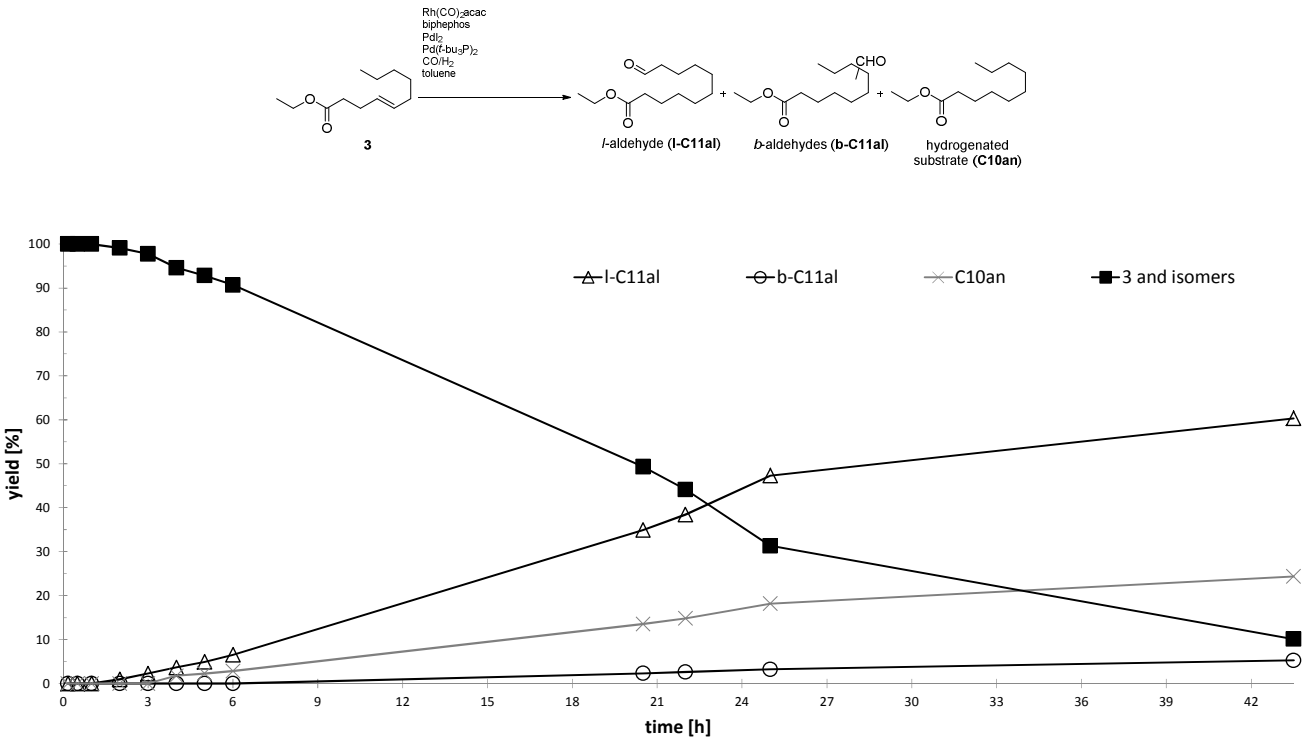


Figure 2. Isomerizing hydroformylation of 4-ethyl decenoate (**3**).

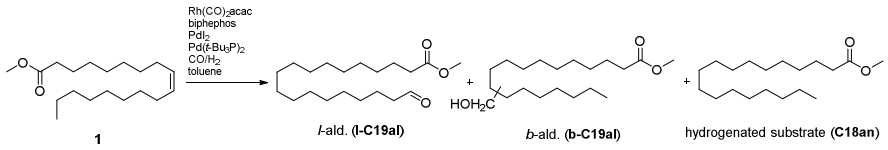
Conditions: 48 g toluene, 40 mmol **3**, 0.4 mol% $Rh(CO)_2acac$, 1.6 mol% biphephos, 0.5 mol% PdI_2, 0.5 mol $Pd(t\text{-}Bu_3P)_2$ 10 bar synthesis gas (absolute pressure, CO/H_2 = 1/1/), 100 °C, batch reaction in 300 mL autoclave, stirrer speed 1000 rpm. Yields were determined by GC-FID.

discussed before, this could also be attributed to the lower concentration of the terminal unsaturated isomer of **3**. For the conversion of long chained fatty acid methyl esters such as methyl oleate, the isomerization rate has to be increased in order to reach reasonable yields and *l*/*b*-ratios.

Isomerizing hydroformylation of methyl oleate (1). As discussed above, a high isomerization rate is required for an efficient conversion of long chained unsaturated esters such as methyl oleate (**1**). When the developed reaction conditions are applied directly in the isomerizing hydroformylation of methyl oleate, almost no reaction was observed (Table 4, Entry 4.1). A higher isomerization rate can be achieved by increasing the temperature or the isomerization catalyst concentration. Studies on model substrate (**2**) showed that increasing the temperature led to high yields of the undesired hydrogenation product and low *l*/*b*-ratios (Figure S1). The same observation was made in the hydroformylation of methyl oleate (Entry 4.2). The yield of the hydrogenated substrate (**C18an**) was 15%, whereas the yield of the targeted linear aldehyde (13% **l-19al**) and also the *l*/*b*-ratio (55/45) of the resulting aldehydes were low. By contrast, higher palladium concentrations led to more promising results (Entry 4.3). When 2 mol% of both Pd-precursors are used at 100 °C, the yield of **l-C19al** was still low (15%) but the *l*/*b*-ratio of the aldehydes was 83/17. Investigations on model substrate **2** showed that the ratio of Pd/I^- strongly influences the activity and selectivity of the reaction (Table 2, entries 2.10 and 2.11). Therefore we examined the Pd/I^- ratio in greater detail for the isomerizing hydroformylation of methyl oleate (**1**) (Table 4, entries 4.3-4.8). The results show that the best yields of **l-c19al** were obtained when the PdI_2 concentration was reduced to 0.33 mol% (Pd/I^- ratio of 3.5, Entry 4.6). The yield of the desired linear aldehyde **l-C19al** was 44% with an *l*/*b*-ratio of 88/12. Higher iodide concentrations led to lower catalyst activity while lower iodide concentrations also led to a strongly decreased *l*/*b*-ratio. After this investigation we set the Pd/I^- ratio to 3.5 and varied the total amount of the isomerization catalyst precursor. It seems that a total palladium concentration of 2.33 mol% is sufficient to allow for a high isomerization rate (Entry 4.6). Higher amounts do not lead to higher yields of desired **l-C19al** (Entry 4.9 and 4.10). Lower concentrations (Entry 4.11) lead to decreased catalytic activity (conversion 40%, yield of **l-C19al** 19% and regioselectivity (*l*/*b* 70/30), indicating that the "supply" of terminal unsaturated esters for the rhodium catalyst is not fast enough. Longer reaction times lead to a higher conversion and higher yields of the desired product **l-C19al.** After 40h, the yield of **l-C19al** was 62% (Entry 4.12), after 72 h full conversion was reached, yielding in 67% **l-C19al** and a *l*/*b*-ratio of the aldehydes of 91/9 (Entry 4.13). These are the highest yields and selectivities described in the literature thus far.

In the absence of the isomerization catalyst (Entry 4.14), yield of the linear aldehyde (3%) and *l*/*b*-ratio (20/80) were drastically lower, clearly demonstrating the benefit of the developed orthogonal tandem catalytic system. It allows for the generation of high aldehyde yields (74%) and regioselectivities (*l*/*b* 91/1) in the hydroformylation.

Table 4: Catalyst development for the isomerizing hydroformylation of methyl oleate (1).



Entry	*T* [°C]	*t* [h]	PdI_2	$Pd(t\text{-}Bu_3P)_2$	Conv.[a] [%]	*l*-ald. (l-C19al) [%]	*b*-ald. (b-C19al) [%]	Hydrogenated substrate (C18an) [%]	*l*/*b*-ratio
4.1[b]	100	16	0.5 mol%	0.5 mol%	4	-	-	4	-
4.2[b]	140	16	0.5 mol%	0.5 mol%	38	13	10	15	55/45
4.3	100	16	2 mol%	2 mol%	31	15	3	13	83/17
4.4	100	16	1 mol%	2 mol%	45	17	3	25	90/10
4.5	100	16	0.5 mol%	2 mol%	55	33	5	17	87/13
4.6	100	16	0.33 mol%	2 mol%	72	44	6	22	88/12
4.7	100	16	0.2 mol%	2 $mol\%_2$	63	37	7	19	84/16
4.8	100	16	-	2.3 mol%	60	31	14	15	70/30
4.9	100	16	1 mol%	6 mol%	71	45	5	21	91/9
4.10	100	16	0.5 mol%	3 mol%	76	46	6	24	88/12
4.11	100	16	0.17 mol%	1 mol%	40	19	9	12	70/30
4.12	100	40	0.5 mol%	3 mol%	93	62	7	24	89/11
4.13	100	72	0.5 mol%	3 mol%	>99	67	7	25	91/9
4.14	100	16	-	-	21	3	12	6	20/80

Conditions: 2.05 g toluene, 1.3 mmol **1**, 0.8 mol% $Rh(CO)_2acac$, 3.2 mol% biphephos, 10 bar synthesis gas (absolute pressure, CO/H_2 = 1/1/), batch reaction in 20 mL autoclave, stirrer speed 500 rpm. Yields were determined by GC-FID.

[a] Double bond isomerization not considered in the conversion.

[b] 0.4 mol% $Rh(CO)_2acac$, 1.6 mol% biphephos

However, the hydrogenation of the substrate is still an issue using the bimetallic catalyst. In order to arrive at a better understanding of the interplay of the orthogonal catalyst system, *in situ* spectroscopic measurements combined with DFT studies should be conducted.[29] This could lead to insights that may prove to be very helpful in the design of new, more efficient orthogonal catalysts.

CONCLUSION

In this paper we describe the successful development of an orthogonal tandem catalytic system for the linear selective isomerizing hydroformylation of methyl oleate. The isomerization catalyst consists of the palladium precursors $Pd(t\text{-}Bu_3P)_2$ and PdI_2 at a ratio of 6/1, while a Rh/biphephos complex is used as the hydroformylation catalyst. The use of this catalyst system leads to an aldehyde yield of 74% and an *l*/*b*-ratio of 91/9 for the resulting aldehydes. These are the highest yields and selectivities described for this reaction in the literature thus far.

EXPERIMENTAL

Chemicals

Toluene (Acros Organics, >99%), ethyl acetate (Acros Organics, >99%), cyclohexane (Acros Organics, >99%) methyl 3-hexenoate (Acros Organics, >95%), ethyl 4-decenoate (TCI Chemicals, >98%) were purchased from different commercial suppliers. Methyl oleate (>89%) was donated by Dako Aktiengesellschaft Chemical Products. Biphephos (>95%) was synthesized from Molisa GmbH. $Rh(CO)_2acac$ was donated by Umicore AG & Co. Kg. Palladium precursors, tri-*tert*-butylphosphine and Lithiumiodid were purchased from ABCR. All chemicals were degassed before use and stored under argon. CO (2.0) and H_2 (5.0) were purchased from Messer Industriegase GmbH.

Hydroformylation reactions

$Rh(CO)_2acac$, $Pd(t\text{-}bu_3P)_2$, PdI_2 and biphephos were weighted either in a homemade 20 ml autoclave or in a 300 ml autoclave (Parr Instruments). The autoclave was closed, evacuated and flushed with argon three times. Degassed toluene and the substrate were subsequently transferred into the reactor via cannula using the standard Schlenk technique. The reactor was pressurized with synthesis gas and heated while stirring to reaction temperature. In cases of time-resolved experiments, samples were taken from the reactor and analyzed via GC-FID. After the reaction time the reactor was put into an ice

bath and the pressure was carefully released. The reaction mixture was analyzed via GC-FID.

Supporting Information.

Additional results regarding the influence of the reaction conditions

Used chemicals

Details about analytical procedures

Product isolation and characterization

NMR and MS spectra

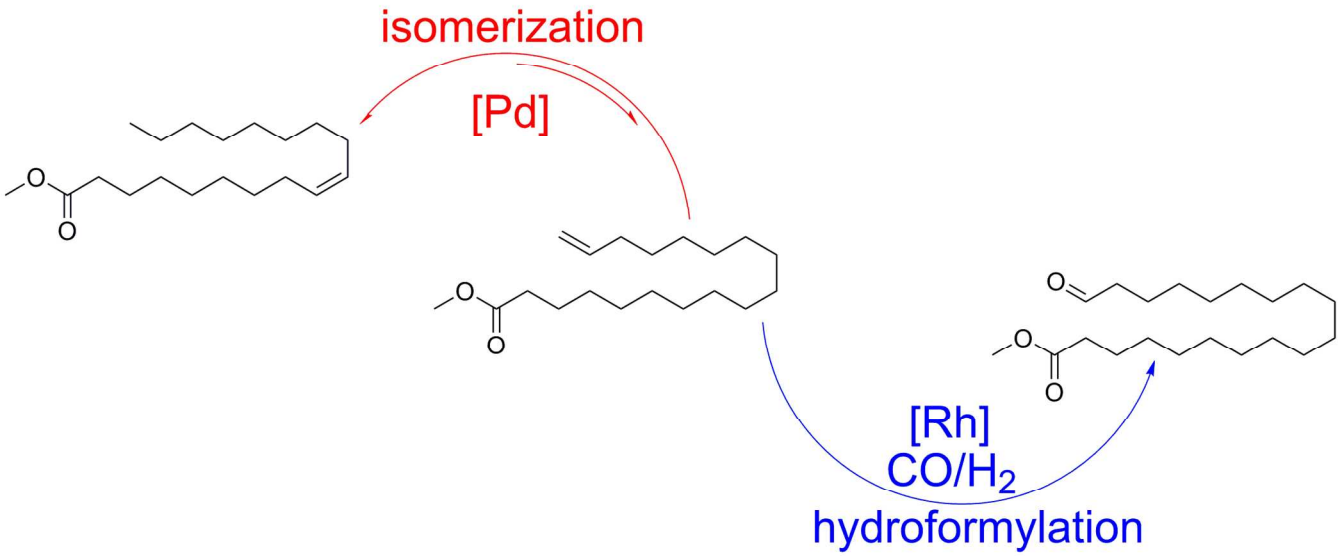
Exemplary chromatograms

ACKNOWLEGMENTS

We gratefully acknowledge the financial support of the German Science Foundation (Project SFB/TRR 63: "InPROMPT – Integrated Chemical Processes in Multi-Phase Fluid Systems") for this work (Subproject A1). We would also like to express our gratitude to Umicore AG & Co. KG for supplying the catalyst precursors and to Dako Aktiengesellschaft Chemical Products for supplying the methyl oleate.

REFERENCES

(1) Kosswig, K. Surfactants. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag, **2000**; pp 431–501.
(2) Cole-Hamilton, D. J. *Angew. Chem., Int. Ed.* **2010**, 49, 8564–8566.
(3) Stempfle, F.; Quinzler, D.; Heckler, I.; Mecking, S. *Macromolecules* **2011**, 44, 4159–4166.
(4) Vilela, C.; Sousa, A. F.; Fonseca, A. C.; Serra, A. C.; Coelho, Jorge F. J.; Freire, C. S.; Silvestre, A. J. *Polym. Chem.* **2014**, 5, 3119–3141.
(5) Walther, G. *ChemSusChem* **2014**, 7, 2081–2088.
(6) Jörke, A.; Seidel-Morgenstern, A.; Hamel, C. *Chem. Eng. J.* **2015**, 260, 513–523.
(7) Roesle, P.; Dürr, C. J.; Möller, H. M.; Cavallo, L.; Caporaso, L.; Mecking, S. *J. Am. Chem. Soc.* **2012**, 134, 17696–17703.
(8) Goldbach, V.; Roesle, P.; Mecking, S. *ACS Catal.* **2015**, 5, 5951–5972.
(9) Jiménez-Rodriguez, C.; Eastham, G. R.; Cole-Hamilton, D. J. *Inorg. Chem. Commun.* **2005**, 8, 878–881.
(10) Roesle, P.; Caporaso, L.; Schnitte, M.; Goldbach, V.; Cavallo, L.; Mecking, S. *J. Am. Chem. Soc.* **2014**, 136, 16871–16881.
(11) Walther, G.; Knöpke, L. R.; Rabeah, J.; Chęciński, M. P.; Jiao, H.; Bentrup, U.; Brückner, A.; Martin, A.; Köckritz, A. *J. Catal.* **2013**, 297, 44–55.
(12) García-Suárez, E. J.; Khokarale, S. G.; van Buu, O. N.; Fehrmann, R.; Riisager, A. *Green Chem.* **2013**, 16, 161–166.
(13) Gaide, T.; Behr, A.; Terhorst, M.; Arns, A.; Benski, F.; Vorholt, A. J. *Chem. Ing. Tech.* **2016**, 88, 158–167.
(14) Gaide, T.; Behr, A.; Arns, A.; Benski, F.; Vorholt, A. J. *Chem. Eng. Process.* **2016**, 99, 197–204.
(15) Jimenez-Rodriguez, C.; Nunez-Magro, A. A.; Seidensticker, T.; Eastham, G. R.; Furst, M. R. L.; Cole-Hamilton, D. J. *Catal. Sci. Technol.* **2014**, 4, 2332–2339.
(16) Witt, T.; Stempfle, F.; Roesle, P.; Häußler, M.; Mecking, S. *ACS Catal.* **2015**, 5, 4519–4529.
(17) van der Veen, Lars A.; Kamer, P. C. J.; van Leeuwen, Piet W. N. M. *Angew. Chem., Int. Ed.* **1999**, 38, 336–338.
(18) Vilches-Herrera, M.; Domke, L.; Börner, A. *ACS Catal.* **2014**, 4, 1706–1724.
(19) Yuki, Y.; Takahashi, K.; Tanaka, Y.; Nozaki, K. *J. Am. Chem. Soc.* **2013**, 135, 17393–17400.
(20) Behr, A.; Obst, D.; Westfechtel, A. *Eur. J. Lipid Sci. Technol.* **2005**, 107, 213–219.
(21) Pandey, S.; Chikkali, S. H. *ChemCatChem* **2015**, 7, 3468–3471.
(22) Vilar, R.; Mingos, D. M. P.; Cardin, C. J. *J. Chem. Soc., Dalton Trans.* **1996**, 25, 4313–4314.
(23) Ohlmann, D. M.; Tschauder, N.; Stockis, J.-P.; Gooßen, K.; Dierker, M.; Gooßen, L. J. *J. Am. Chem. Soc.* **2012**, 134, 13716–13729.
(24) Baader, S.; Podsiadly, P. E.; Cole-Hamilton, D. J.; Gooßen, L. J. *Green Chem.* **2014**, 16, 4885–4890.
(25) Baader, S.; Ohlmann, D. M.; Gooßen, L. J. *Chem. - Eur. J.* **2013**, 19, 9807–9810.
(26) Gooßen, L.; Arndt, M.; Mamone, P.; Gruenberg. WO2013000874 A1, **2013.**
(27) Mamone, P.; Gruenberg, M. F.; Fromm, A.; Khan, B. A.; Gooßen, L. J. *Org Lett.* **2012**, 14, 3716–3719.
(28) Jörke, A.; Seidel-Morgenstern, A.; Hamel, C. *J. Mol. Catal. A: Chem.* **2017**, 426, 10–14.
(29) Li, C.; Chen, L.; Garland, M. *J. Am. Chem. Soc.* **2007**, 129, 13327–13334.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[Pd]
[Rh]
CO/H2
hydroformylation

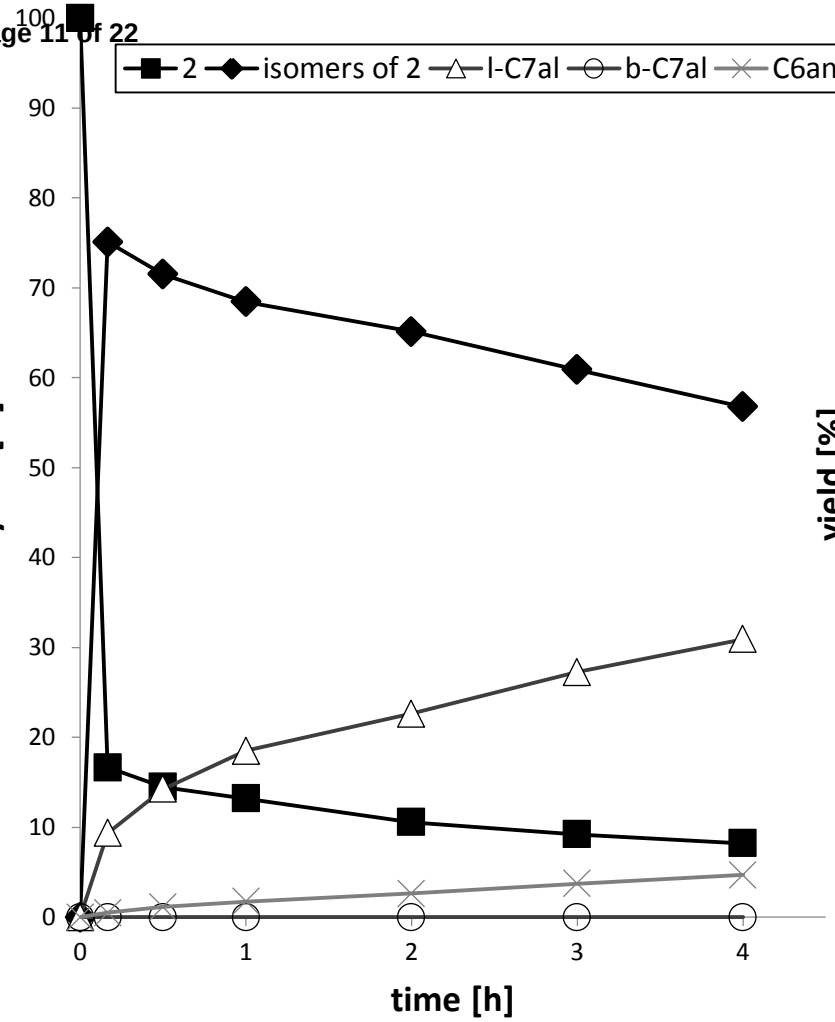


Figure 1a. Rh/biphephos/PdI_2/Pd(*t*-$Bu_3P)_2$ at 100 °C

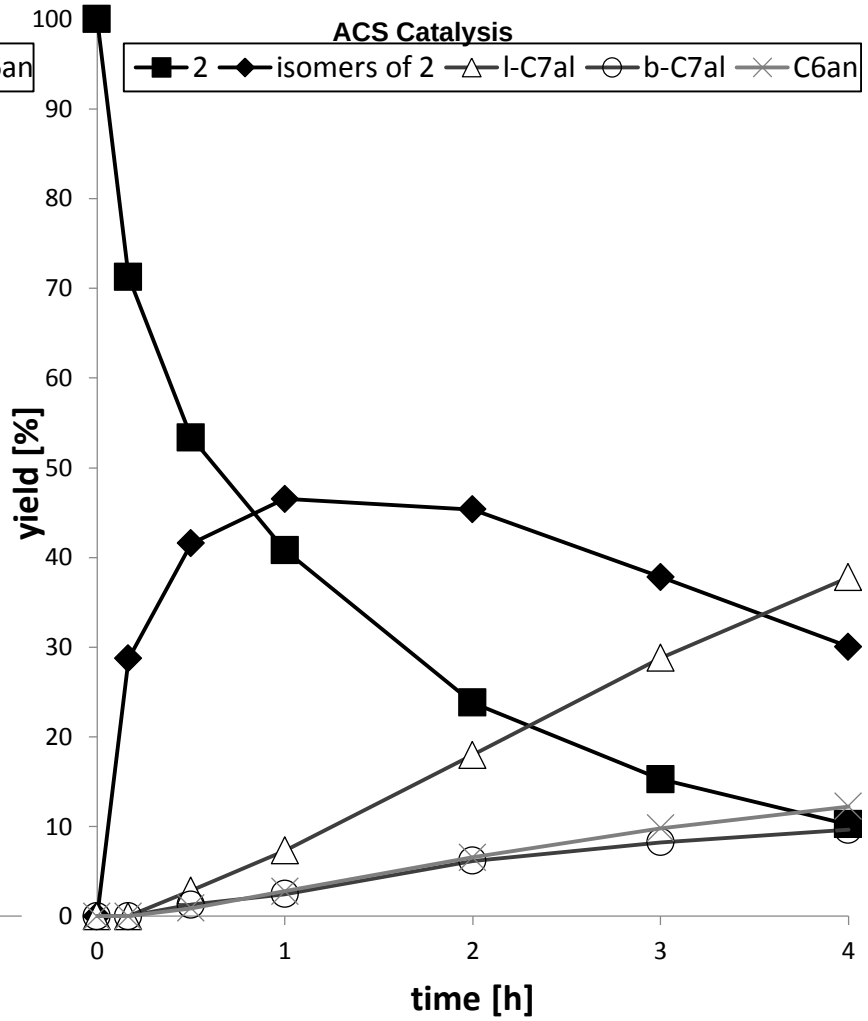


Figure 1b. Rh/biphephos at 90 °C

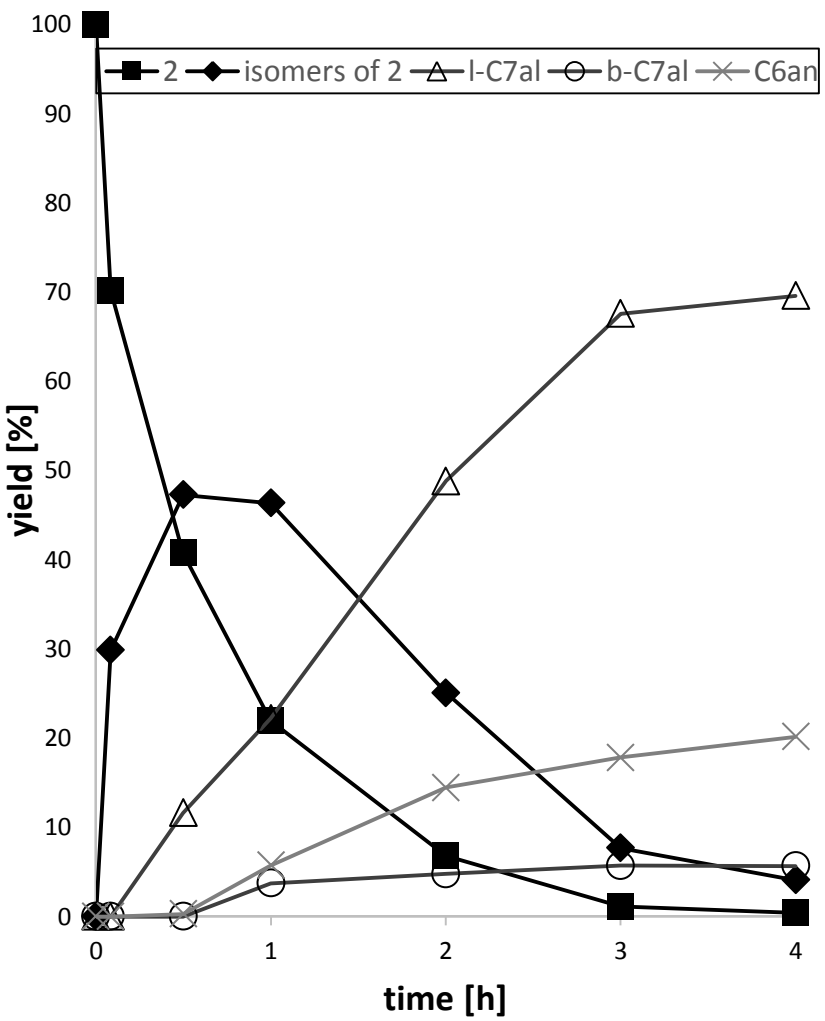
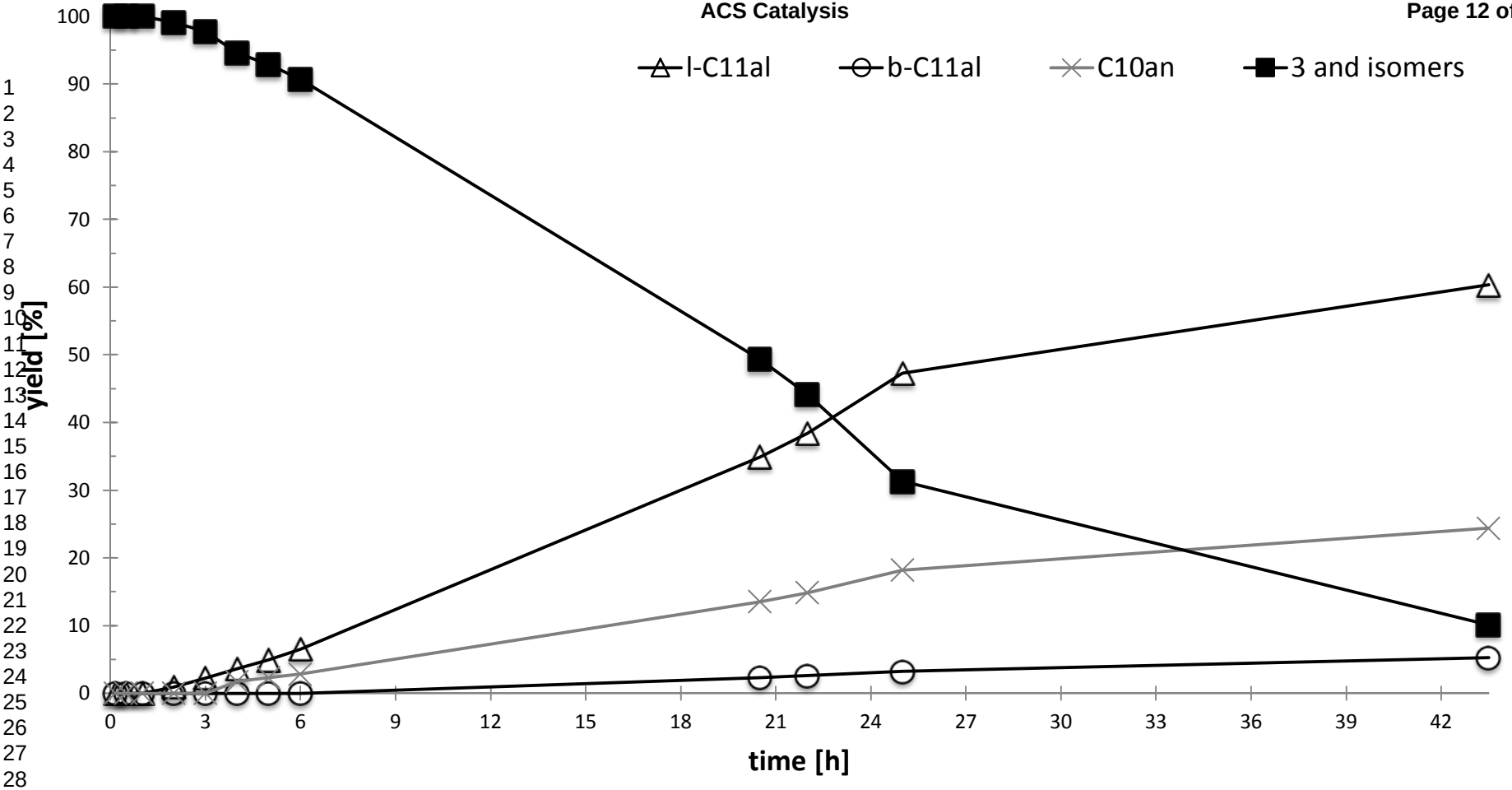


Figure 1c. Rh/biphephos at 100 °C


l-C11al
b-C11al
C10an
3 and isomers
yield [%]
time [h]
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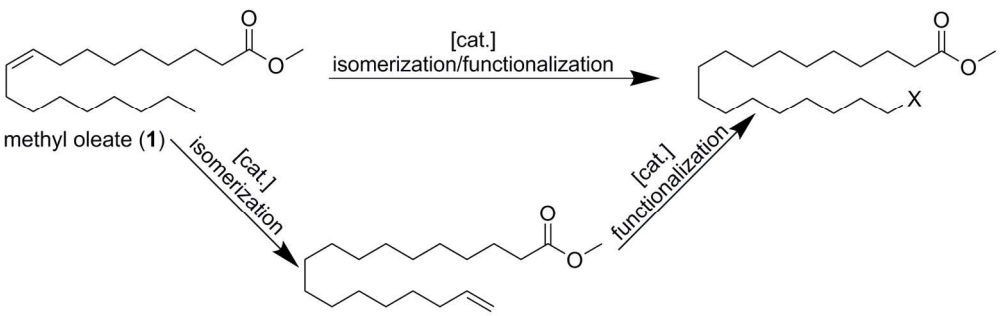

Scheme 1: Isomerization / -functionalization of methyl oleate (1).

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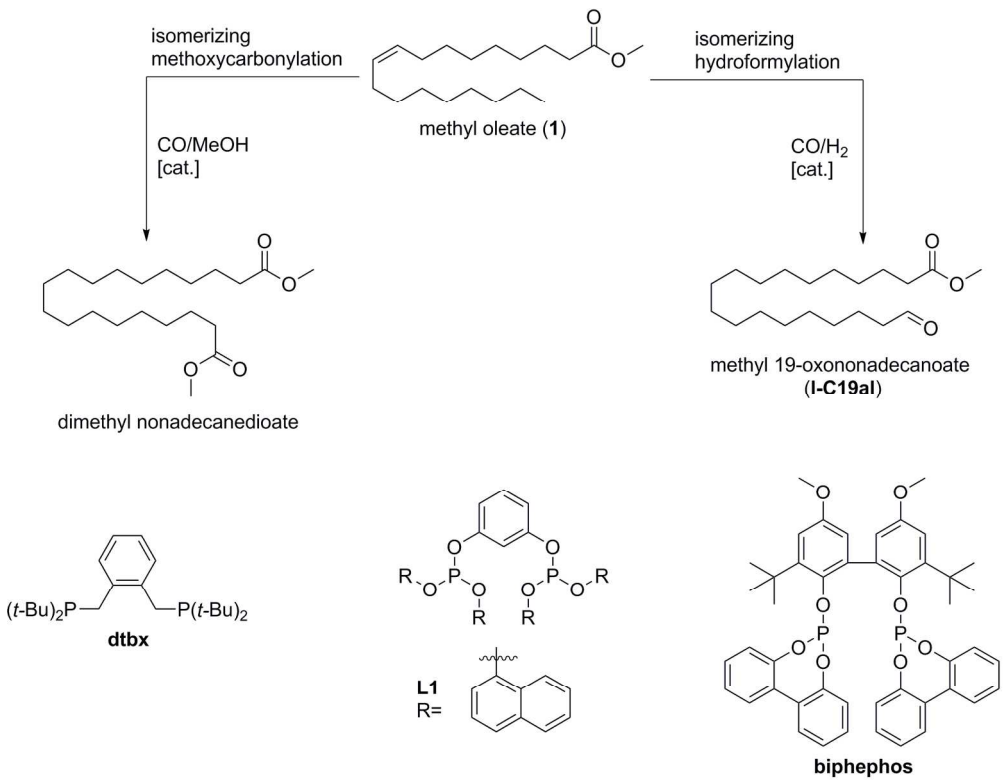

Scheme 2: Isomerizing hydroformylation and meth-oxycarbonylation.

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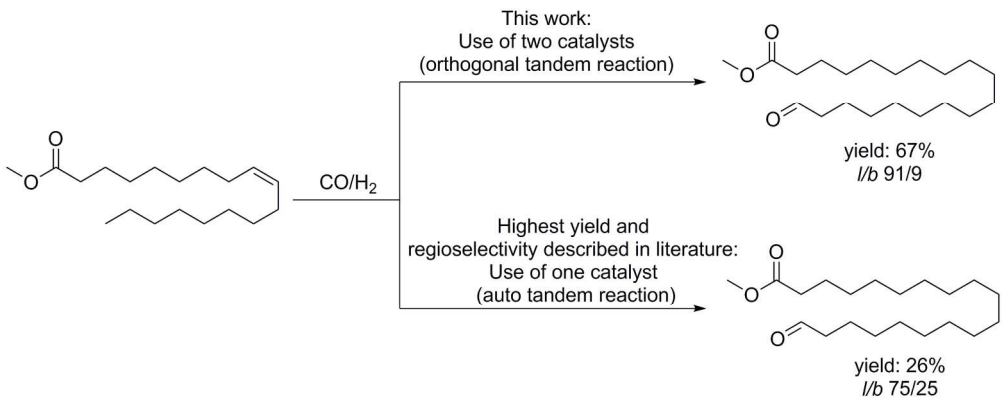

Scheme 3. Isomerizing hydroformylation of methyl oleate: This work compared with literature.

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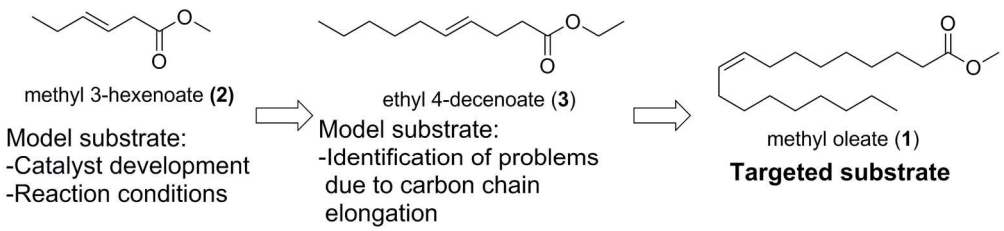

Scheme 4: Approach for development of the isomer-izing hydroformylation of FAMEs.

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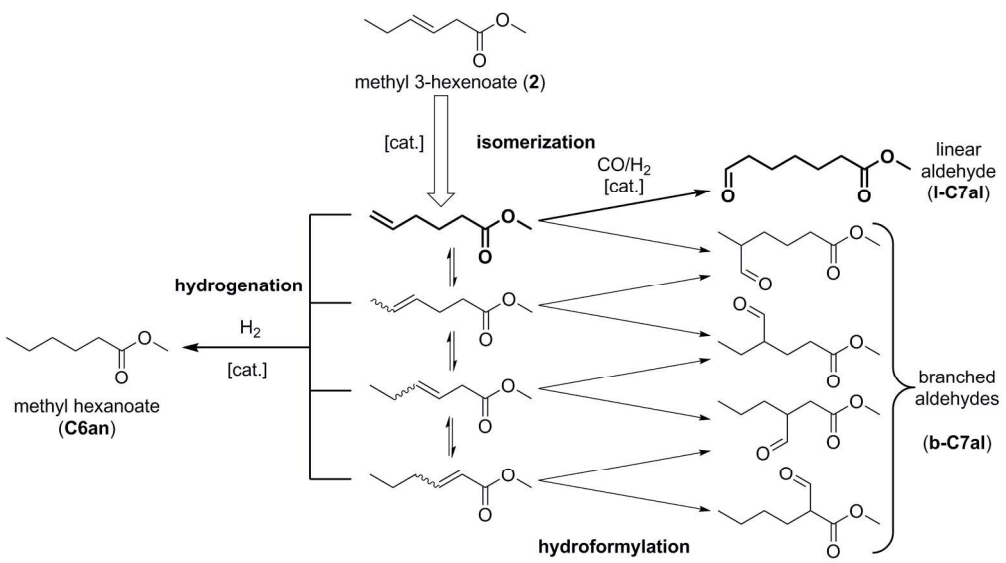

Scheme 5: Reaction network of the isomerizing hy-droformylation of 2.

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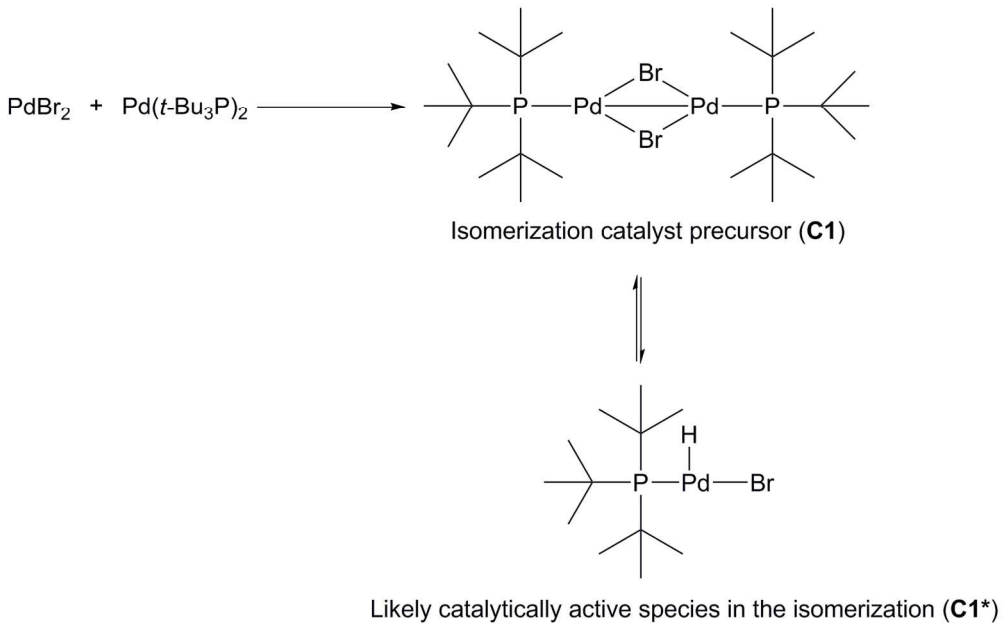

Scheme 6: Synthesis of C1 and likely catalytically active species according to Gooßen et al.

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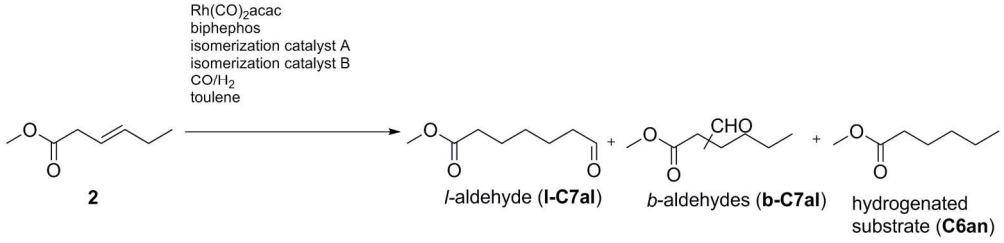

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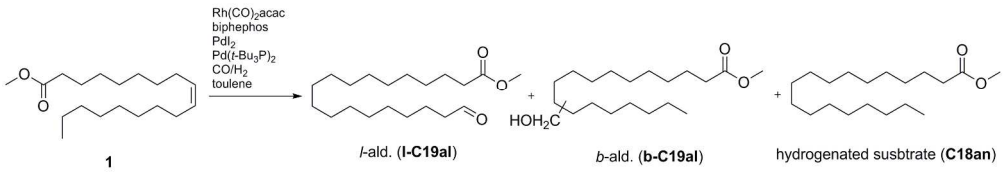

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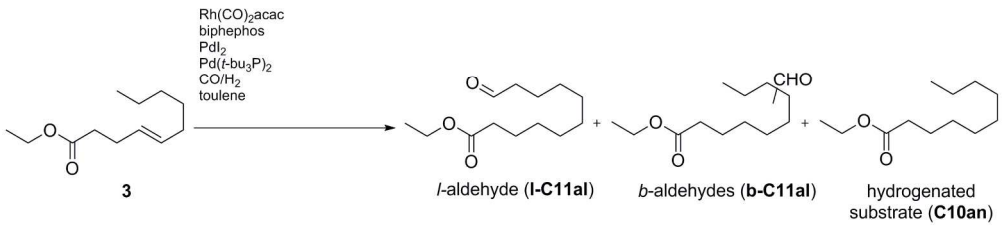

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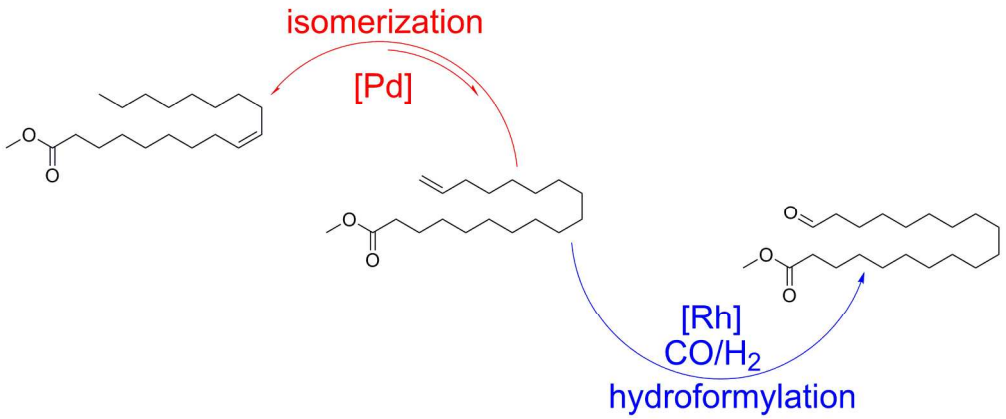

TOC

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