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# Catalytic Isomerizing $\omega$-Functionalization of Fatty Acids

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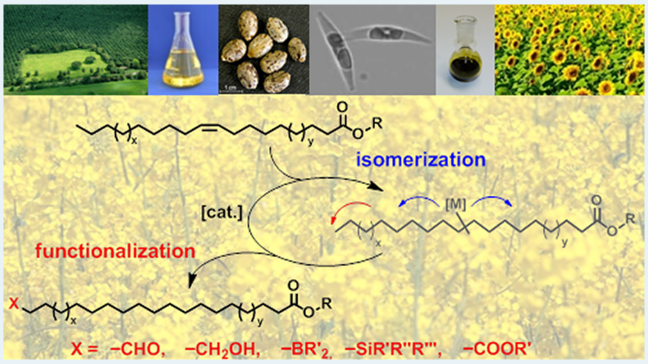
**ABSTRACT:** Isomerizing functionalization reactions that convert the internal double bonds of unsaturated fatty acids from plant or algae oils to a terminal functional group are attractive because they can generate linear long-chain $\alpha,\omega$-difunctional compounds that incorporate the entire length of the substrates chain. The state of the art toward this formidable synthetic challenge via different catalytic approaches, namely isomerizing borylations, silylations, and carbonylations (and for comparison, olefin metathesis) is reviewed comprehensively and analyzed with regard to underlying mechanistic principles, performance, practicability, and scope.



**KEYWORDS:** *isomerizing functionalization, transition metal catalysis, fatty acids, hydroformylation, hydroboration, silylation, alkoxycarbonylation, olefin metathesis*

## INTRODUCTION

Fatty acids from plant oils are a unique feedstock for the production of chemicals because of their characteristic long-chain methylene sequences.[1,2] These fatty acids are already endowed with a functional group in the form of the carboxyl unit. For many applications, a further functionality is required. The double bonds of unsaturated fatty acids offer themselves for the generation of additional functional groups. Such mono- or multiple unsaturated fatty acids are contained in substantial amounts in common plant oils (Table 1).[3]

Table 1. Fatty Acid Composition of Selected Plant Oils[a,2,3]

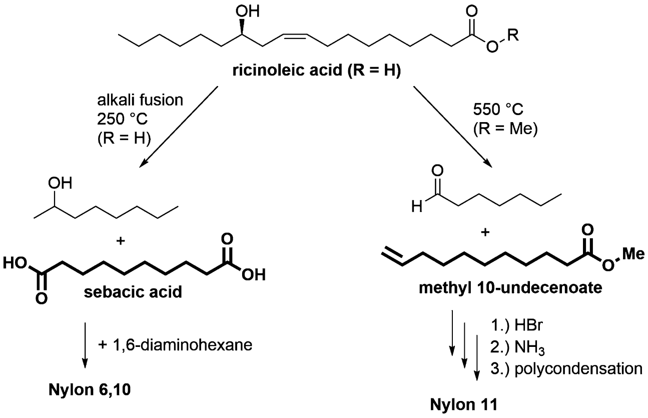
| plant oil | double bonds[b] | palmitic[c] (16:0) (%) | stearic[c] (18:0) (%) | oleic[c] (18:1) (%) | linoleic[c] (18:2) (%) | linolenic[c] (18:3) (%) |
|---|---|---|---|---|---|---|
| palm oil | 1.7 | 43 | 4 | 41 | 10 | – |
| rapeseed | 4 | 4 | 2 | 56 | 26 | 10 |
| soybean | 5 | 11 | 4 | 23 | 53 | 8 |
| sunflower | 5 | 5 | 3 | 37 | 54 | 1 |
| HO-sunflower[d] | 3.0 | 2 | 1 | 93 | 2 | – |

[a]wt % of a given fatty acids with respect to total fatty acid content. [b]Average number of double bonds per triglyceride. [c]Number of carbon atoms and double bonds given in parentheses. [d]HO = high oleic.

Illustrative examples to this end are the longstanding utilizations of ricinoleic acid, the major component (up to 90%) of castor oil, for the generation of polycondensation monomers.[4] Alkali fusion of ricinoleic acid at elevated temperatures (250 °C) yields sebacic acid along with stoichiometric amounts of 2-octanol as a coupling product.[5] Polycondensation of sebacic acid with 1,6-diaminohexane produces nylon-6,10 (Scheme 1; left pathway). By thermally induced rearrangement of methyl ricinoleate, methyl 10-undecenoate is obtained along with stoichiometric amounts of heptanal as a coupling product. Further transformation of methyl 10-undecenoate with hydrobromic acid and ammonia yields 11-aminoundecanoic acid, which is polymerized to produce nylon-11, that is commercially available under its trade name "Rilsan" (Scheme 1, right pathway).[6]

These particular rearrangement and C−C cleavage reactions are, however, restricted to fatty acids with a hydroxy group in the vicinity of the double bond, of which ricinoleic acid is the

Scheme 1. Monomer and Polymer Generation from Castor Oil-Based Ricinoleic Acid and Its Methyl Ester by Alkali Fusion (left pathway) and Thermal Rearrangement (right pathway)



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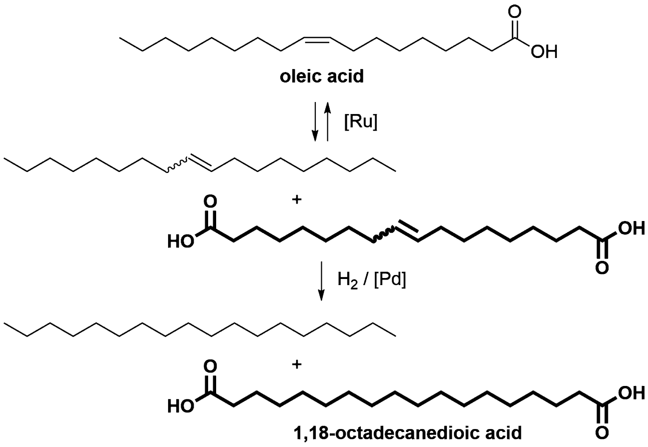
only practically available representative. Instead, ozonolysis of oleic acid yields azelaic acid along with stoichiometric amounts of pelargonic acid as a coupling product.[7−9] This process is also performed on an industrial scale.[10]

An alternative to ozonolysis is provided by oxidative cleavage of the double bond of methyl oleate with hydrogen peroxide as an oxidant in the presence of a ruthenium catalyst, yielding azelaic acid mono methyl ester and stoichiometric amounts of pelargonic acid as a coupling product.[11] In all these processes, only a part, roughly half, of the fatty acid chain is incorporated into the resulting mid-chain *α*,*ω*-difunctional product. The rest is lost as a coupling product of less value. In addition, the full potential of the long methylene sequences of the fatty acid feedstock to impart useful properties such as hydrophobicity or crystallinity is not utilized. The attractiveness of such an approach is demonstrated by recent studies of semicrystalline aliphatic polyesters[12−16] hydrophobic polyamides,[13] and hydrolytically degradable polyacetals from long-chain linear monomers.[17,18] This underlines the need for efficient routes for the generation of long-chain difunctional compounds X−$(CH_2)_n$−Y that incorporate the full length of the fatty acid chain.

In principle, such long-chain *α*,*ω*-functionalized compounds can be generated from plant oils by olefin metathesis reactions.[2,19,20] Self-metathesis of oleic acid with Grubbs or Hoveyda−Grubbs catalysts can yield 1,18-octadecanedioic acid (after subsequent hydrogenation of the double bond);[2,19,21] however, isomerization of the starting materials' double bond by decomposition products of the ruthenium catalyst may result in a mixture of dicarboxylic acids with different chain lengths.[21] More importantly, metathesis of, for example, oleic acid yields stoichiometric amounts of the $C_{18}$-alkene (Scheme 2), and conversions are limited as a result of the thermodynamic control of the reaction. As an equilibrium reaction, the conversion can reach 50% at its maximum unless one of the products can be removed from the reaction mixture selectively. Note that highly purified oleic acid is needed for a clean conversion to 1,18-octadecenedioic acid. The presence of fatty acids with different numbers of carbon atoms or double bonds (cf. Table 1)[2,3] as contained in typical plant oils will result in a complex mixture of products with different chain lengths. Other than self-metathesis, cross-metathesis of fatty acids with lower molecular weight nonfunctionalized olefins, such as ethylene,[22−27] generates an olefin and a monofunctionalized unsaturated product by splitting the fatty acid derivate at the internal double bond. Cross-metathesis with functionalized olefins, for example, 3-hexenedioic acid,[28] can introduce an additional functionality to the fatty acid feedstock. However, as in the aforementioned chain cleavage reactions, only mid-chain *α*,*ω*-difunctional products are formed along with stoichiometric coupling products.

In summary, all these approaches incorporate only a part of the fatty acid feedstock into *α*,*ω*-difunctionalized products, and stoichiometric amounts of less valuable coupling products are formed. In principle, a variety of (catalytic) functionalization reactions that do not go along with cleavage of the fatty acid chain offer themselves for the functionalization of the double bonds. Epoxidations are an established example. Incorporating the entire length of the fatty acid chain into *α*,*ω*-functionalized compounds is a challenge, however. This requires the conversion of a double bond located deep in the fatty acid chain of the starting material to a terminal functional group.[9,10,29] Therefore, a preceding isomerization step is necessary, followed by an efficient and selective functionalization in the terminal position. Such a terminal functionalization of long-chain compounds, such as methyl oleate, with high conversion and selectivity is particularly difficult because an equilibrium mixture of an isomerized fatty acid ester contains less than 0.2% of the terminal olefin (vide infra).

**Scheme 2. Self-Metathesis of Oleic Acid Yielding 1,18-Octadecanedioic Acid**



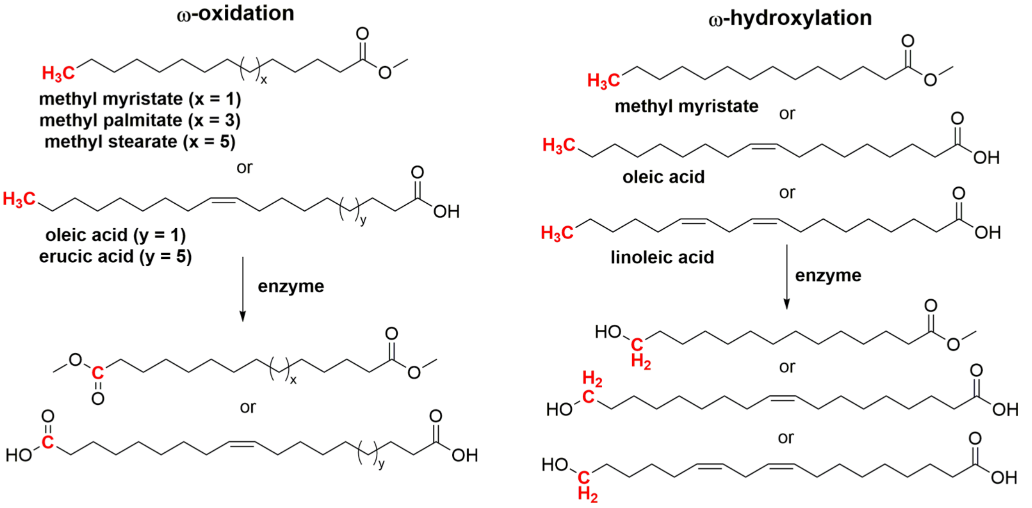
## SELECTIVE *ω*-FUNCTIONALIZATION OF FATTY ACIDS

A selective *ω*-functionalization of fatty acids can be achieved, among others, by biotechnological pathways.[30,31] Via selective enzymatic *ω*-oxidation of the terminal methyl group using the yeast *Candida tropicalis*, it is possible to transform saturated and unsaturated fatty acids into the respective *α*,*ω*-functionalized diacids.[32−35] Engineered *C. tropicalis* is capable of selective terminal oxidation of methyl myristate (14:0), methyl palmitate (16:0), methyl stearate (18:0), oleic acid (18:1), and erucic acid (22:1) to the respective dicarboxylic acids (Scheme 3, left).[32−34] The position and configuration of the double bonds are maintained in unsaturated substrates. Further engineering, namely, the elimination of enzymes that are responsible for the oxidation of the intermediately formed *ω*-hydroxy group, allowed for the selective synthesis of *ω*-hydroxy-functionalized methyl myristate (14:0). Other fatty acids (methyl palmitate (16:0), methyl stearate (18:0), oleic acid (18:1), and linoleic acid (18:2)) were also transformed into the respective *ω*-hydroxy fatty acids, although with a lower selectivity and productivity (Scheme 3, right).[35]

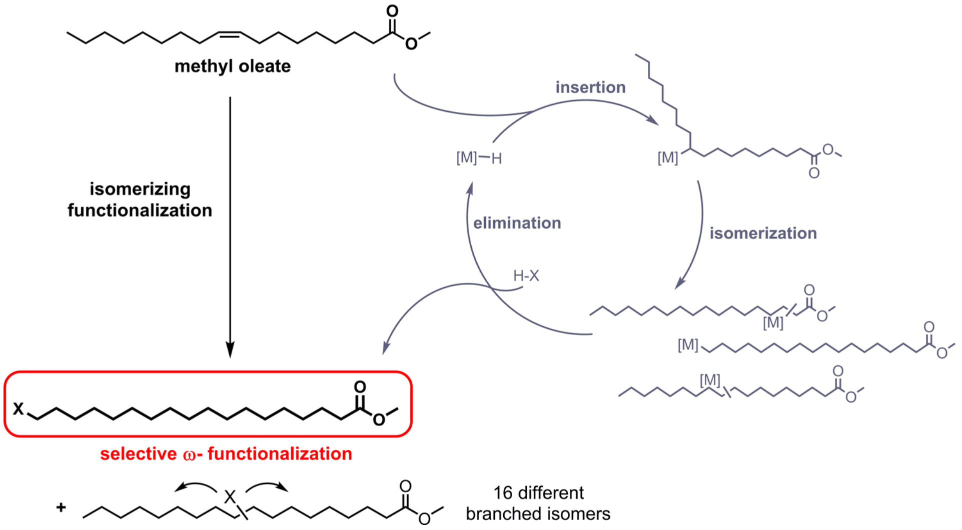
A limitation of these biotechnological pathways is the necessity of feeding costly glucose to the yeasts as a result of the blocked *β*-oxidation pathway, which usually delivers energy needed for these biotechnological processes. In addition, complex downstream processing is necessary to extract the desired product.

Regarding these issues, entirely chemical catalytic pathways are attractive alternative approaches.[36,37] Selective isomerization and *ω*-functionalization of the double bond of unsaturated fatty acids can, in principle, incorporate the entire fatty acid chain into the desired linear *α*,*ω*-functionalized product (Scheme 4); however, this is difficult because terminal olefins are thermodynamically strongly disfavored versus the internal double bonds of the substrate. In particular, *α*,*β*-unsaturated esters are slightly favored, because of the conjugated double bond system, compared with other double

Scheme 3. Selective $\omega$-Oxidation (left) and $\omega$-Hydroxylation (right) of Fatty Acids via Enzymatic Pathways to $\alpha,\omega$-Difunctionalized Compounds



Scheme 4. General Reaction Scheme of Metal-Catalyzed (M) Isomerizing $\omega$-Functionalization of Unsaturated Fatty Acids Yielding Linear Long-Chain $\alpha,\omega$-Difunctional Compounds and Other Isomers with the Functional Group Distributed over All Positions along the Chain (exemplified with methyl oleate)

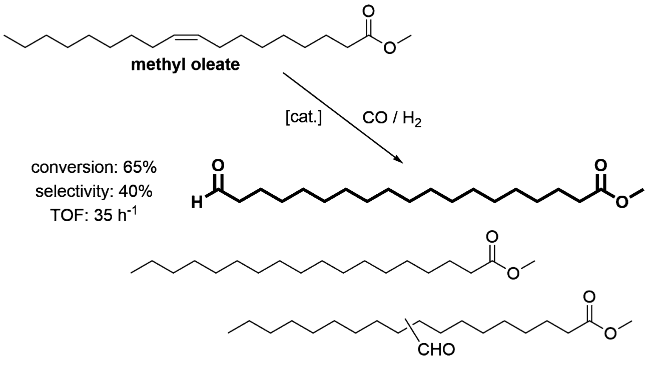


bond isomers. For methyl oleate, 94.3% of internal olefins, 5.5% of $\alpha,\beta$-unsaturated ester, and <0.2% of terminal olefin are found in the equilibrium mixture of all isomers.[38] The challenge is to find ways to functionalize the terminal isomer exclusively out of a mixture of all isomers. An effective suppression of the numerous other pathways on the various olefins, including the $\alpha,\beta$-unsaturated ester, is required to achieve a high selectivity toward the linear $\alpha,\omega$-difunctionalized compound (Scheme 4). Hydroboration is a straightforward example with a clear preference for terminal functionalization because this yields the thermodynamically most stable isomer here. Other approaches to achieve terminal functionalization take advantage of a high kinetic preference for the terminal reaction pathway.

We review catalytic isomerizing functionalization approaches for the transformation of fatty acids into linear $\alpha,\omega$-functionalized compounds. As far as they are instructive toward this aim, additionally isomerizing functionalizations of other internal olefins with a double bond remote from the terminal site of functionalization, such as 4-octene, are also considered and discussed, in particular for functionalization reactions for which transformations of fatty acids have been less studied so far.

**Isomerizing Hydroformylation.** Hydroformylation is perhaps the most prominent and definitely one of the largest homogeneously catalyzed reactions in the chemical industry. Relevant catalysts are based on cobalt or rhodium bearing phosphorus ligands, but platinum, palladium, ruthenium and iron have also been reported. With regard to the generation of linear $\alpha,\omega$-functionalized compounds, isomerizing hydroformylation of fatty acids can provide such linear long-chain compounds bearing an $\omega$-aldehyde group (Scheme 5). Börner and co-workers recently reviewed the isomerizing hydroformylation.[39] A large number of studies addressed the isomerizing hydroformylation of 2-olefins (e.g., 2-butene, 2-pentene, 2-hexene, or 2-octene).[40−50] Furthermore, Carpentier and co-workers presented the hydroformylation of fatty acid-derived substrates, such as 10-undecenenitril, with a high linear selectivity and the ability to convert internal isomers of the starting material to the desired linear aldehyde.[51,52] However, the reactivity of these olefins with the double bond at or adjacent to the chain terminus differs substantially from olefins with the double bond deep in the chain, as discussed later in more detail with several examples of rhodium-catalyzed hydroformylation of octenes (vide infra). Concerning the scope reviewed here, the transformation of more challenging substrates is of interest because these are potentially directly instructive for the synthesis of linear $\alpha,\omega$-functionalized compounds from plant oils by isomerizing $\omega$-functionalization. Thus, isomerizing hydroformylation of substrates in which the double bond is three or more carbon atoms away from the terminus (e.g., 4-octene) are considered exclusively, in addition to fatty acids themselves.

**Scheme 5. Isomerizing Hydroformylation of Methyl Oleate to the Desired $\omega$-Aldehyde Ester and Relevant Byproducts**[a]



[a]For values of conversion, selectivity and TOF, see ref 64.

*Platinum-Based Catalysts.* Tang and co-workers reported the isomerizing hydroformylation of *trans*-5-decene using a cationic platinum complex $[PtCl(CO)(P(OPh)_3)_2]ClO_4$ with a metal halide (e.g., $SnCl_2{\cdot}2H_2O$) as a catalyst precursor at 100 °C and 140 bar (1 mol % Pt, 5 mol % Sn, $CO/H_2 = 1/1$).[53] After 3 h, the olefin conversion was 73%, with 84% aldehyde selectivity but a relatively low aldehyde linearity of only 17% (this corresponds to an average turnover frequency (TOF) of 26 $h^{-1}$). As a side reaction, 16% of the hydrogenation product decane was formed. The authors also stated that combination of the well-known hydroformylation catalyst system $[PtCl_2(PPh_3)_2]/SnCl_2$ with compounds promoting isomerization (e.g., acids, base, inorganic or organometallic compounds) did not result in formation of the terminal aldehyde, even though isomerization was observed in some cases. Vogt and co-workers gave another example for platinum-catalyzed isomerizing hydroformylation using 0.1 mol % of $[Pt(SiXantPhos)Cl(SnCl_3)]$ as the catalyst precursor.[54] With 4-octene as the substrate, a conversion of 19% was observed. Formation of 33% 1-nonanal along with 16% branched aldehydes, 11% octane, and 40% isomerized octenes as side products at 100 °C and 10 bar ($CO/H_2 = 1/1$) after 15 h of reaction time was noted. This corresponds to a selectivity of 55% to the linear aldehyde and an average TOF of 13 $h^{-1}$. Hydrogenolysis of the intermediately formed Pt−acyl species was identified as the rate-limiting step at temperatures above 40 °C. In general, catalyst activity and selectivity increased with increasing temperature. However, hydrogenation also became more significant at higher temperatures (>70 °C).

*Cobalt-Based Catalysts.* Beck and co-workers compared the selectivity in the $Co_2(CO)_8$-catalyzed (isomerizing) hydroformylation of 1-octene, *cis*-4-octene, and *trans*-4-octene at 120 °C and 200 bar (2.5 mol % Co, $CO/H_2 = 1/1$).[55] Selectivities of 74%, 54%, and 56% toward the linear aldehyde 1-nonanal at conversions of 66%, 60%, and 52%, respectively, were observed. This work clearly shows that the unmodified cobalt catalyst precursor $Co_2(CO)_8$ is suitable for isomerizing hydroformylation with a preference for terminal functionalization. Although cobalt plays an important role in hydroformylation in general, most examples of isomerizing hydroformylation use rhodium-based catalysts (vide infra).

*Rhodium-Based Catalysts.* Generally, rhodium-catalyzed hydroformylation has some major advantages over cobalt-based systems. Rhodium catalysts are usually active under milder conditions, for example, lower temperatures and pressures, and exhibit higher activity, as well as increased selectivity toward the desired linear products.

Van Leeuwen and co-workers reported the rhodium-catalyzed isomerizing hydroformylation of *trans*-4-octene with bidentate dibenzophosphindole- and diphenoxaphosphinine-substituted xanthene ligands **1a** and **1b** (Figure 1, Rh/ligand = 1/10; 0.15 mol % Rh, Table 2, entry 1, 2).[56] Both rhodium diphosphane complexes showed a high selectivity toward the linear aldehyde 1-nonanal with good conversions at 120 °C and 2 bar ($CO/H_2 = 1/1$). The catalyst system with ligand **1b** was more active (Table 2, entry 2), but at the same time selectivity decreased compared with **1a**. An initial TOF (20−30% conversion) of 15 $h^{-1}$ for **1a** and 20 $h^{-1}$ for **1b** was reported. In their study, isomerizing hydroformylation of *trans*-2-octene as a substrate was also investigated, and a higher selectivity to the linear aldehyde and a higher initial TOF compared with 4-octene was observed. On the basis of these results, the authors suggested that the applied rhodium complexes exhibit a low isomerization activity, and therefore, turnover frequencies for internal olefins are low. It was also stated that no hydrogenation was observed, and hydroformylation of the terminal olefin was preferred.

Selent and co-workers reported the rhodium-catalyzed formation of 1-nonanal from a mixture of isomeric *n*-octenes by using monodentate phosphonite ethers as a ligand (0.006 mol % Rh, Rh/ligand = 1/10) at 140 °C and 20 bar ($CO/H_2 = 1/1$). The hydroxyl phosphonite ligand **2** showed a superior selectivity toward 1-nonanal compared with a methyl ether analogue (Table 2, entry 8).[57,58] An initial TOF (20% conversion) of 1320 $h^{-1}$ was observed, and hydrogenated olefin (total yield <1.4%) and hydrogenated aldehyde (total yield = 1.4%) as side products were reported. Higher TOFs up to 19 000 $h^{-1}$ were reached with increased ligand loadings (Rh/ligand = 1/50). Selectivity toward the linear aldehyde was lower compared with van Leeuwen's catalyst, but catalyst activity was significantly higher. A further increase in the reaction rate was reported later, with bidentate phosphonites as ligands for isomerizing hydroformylation under slightly different reaction conditions (130 °C and 0.06 mol % rhodium). The bidentate phosphonite ligand **3** showed the best results, with an increased yield and selectivity to 1-nonanal with a remarkably high turnover frequency of 4448 $h^{-1}$ (20% conversion) and reduced hydrogenation activity (total yield of hydrogenated aldehyde = 0.3%, Table 2, entry 9).[59]

Beller and co-workers reported the rhodium-catalyzed isomerizing hydroformylation of 4-octene in the presence of 2,2′-bis(3,4,5-trifluorobenzyl)-1,1′-binaphthalene **4** as a ligand (0.01 mol % Rh, Rh/ligand = 1/5) at 120 °C and 10 bar ($CO/H_2 = 1/1$, Table 2, entry 7).[60] A selectivity of 70% to the linear

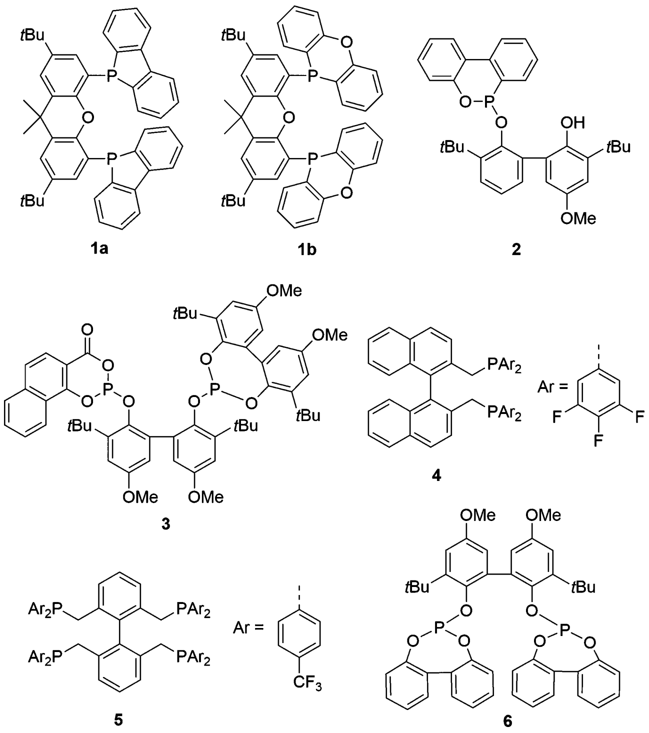


**Figure 1.** Phosphorus-based ligands for Rh-catalyzed isomerizing hydroformylation of internal alkenes.

**Table 2. Rhodium-Catalyzed Isomerizing Hydroformylation**

| entry | olefin | conversion (%) | selectivity[a] (%) | TOF[b] ($h^{-1}$) | ref |
|---|---|---|---|---|---|
| 1 | *trans*-4-octene[c] | 54 | 86 | 15 | 56 |
| 2 | *trans*-4-octene[d] | 67 | 81 | 20 | 56 |
| 3 | *trans*-4-octene | 60 | 66 | 300ø | 61 |
| 4 | *trans*-4-octene[e] | 82 | 89 | 41ø | 62, 63 |
| 5 | *trans*-4-octene[f] | 94 | 95 | 34[g] | 62 |
| 6 | *cis*-4-octene | 59 | 47 | 295ø | 61 |
| 7 | 4-octene | 41 | 70 | 43 | 60 |
| 8 | isomeric *n*-octenes[h,i] | 55 | 48 | 1320 | 57 |
| 9 | isomeric *n*-octenes[h,j] | 96 | 69 | 4448 | 59 |
| 10 | methyl oleate | 65 | 40 | 35ø | 64 |

[a] Selectivity toward the linear aldehyde. [b] Turnover frequency (TOF) is given at 20−30% conversion if information available from reference; if not available, TOF is averaged over complete reaction time with given conversion (ø); see reference for details. [c] Rh-precursor [Rh(CO)$_2$(dipivaloylmethanoate)], ligand **1a**, Rh/ligand = 1/10. [d] Rh-precursor see c, ligand **1b**, Rh/ligand = 1/10. [e] Toluene as organic solvent. [f] Propylene carbonate as organic solvent, liquid−liquid two-phase reaction. [g] TOF for two-phase reaction system was determined after complete conversion of olefin to aldehyde. [h] Isomeric *n*-octenes: 3.3% 1-octene, 48.4% *cis*/*trans*-2-octene, 29.2% *cis*/*trans*-3-octene, 16.4% *cis*/*trans*-4-octene. [i] 0.006 mol % [Rh(acac)(cod)], ligand **2**, Rh/ligand = 1/10. [j] 0.06 mol % [Rh(acac)(cod)], ligand **3**, Rh/ligand = 1/10.

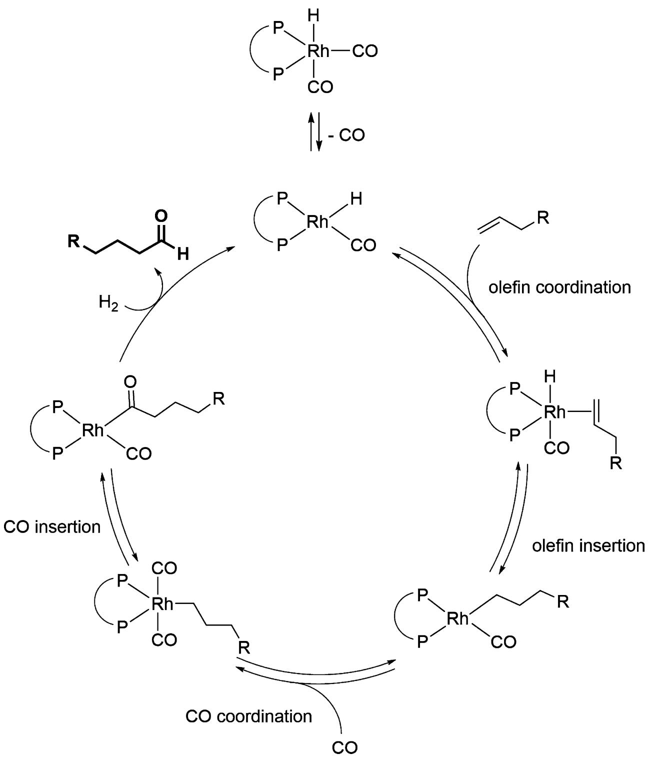
aldehyde 1-nonanal was observed at 41% conversion after a reaction time of 96 h. Using 2-octene as a starting material resulted in a higher conversion (64%) and selectivity (88%), which was also observed by van Leeuwen with his catalyst system (vide supra). Isomerization of 4-octene was slow, and hydroformylation of the internal double bond occurred faster.

Zhang and co-workers reported the rhodium/tetraphosphine (**5**) catalyzed isomerizing hydroformylation of *cis*- and *trans*-4-octene at 125 °C and 10 bar (0.1 mol % Rh, Rh/ligand = 1/4, CO/H$_2$ = 1/1, Table 2, entry 3, 6).[61] Within a reaction time of 2 h, 59% of *cis*-4-octene was converted into aldehydes with a selectivity of 47% to 1-nonanal (Table 2, entry 6). For *trans*-4-octene, conversion into aldehydes was slightly higher, with increased selectivity to the desired linear product (Table 2, entry 3). The methyl-branched aldehyde was the major hydroformylation byproduct, and only small quantities of octane were formed. Note that when 2-octene was used instead of 4-octene, conversion (84%) and selectivity to the linear aldehyde (98%) were significantly higher under otherwise identical conditions. This and all aforementioned studies showed that isomerization of a double bond adjacent to the chain terminus occurs much faster compared with isomerization over three or more carbon atoms.

Behr and co-workers reported the isomerizing hydroformylation of *trans*-4-octene by a rhodium/BiphePhos **6** (ratio = 1/3) catalyst system at 125 °C and 20 bar (CO/H$_2$ = 1/1) in 89% selectivity to the linear aldehyde (Table 2, entry 4).[62,63] Applying 0.5 mol % Rh, 82% of the substrate was converted, yielding 75% 1-nonanal, along with 3% octane and 4% branched aldehydes after a reaction time of 4 h. A further increase in conversion and selectivity toward 1-nonanal was achieved by using propylene carbonate instead of toluene, forming a liquid−liquid two-phase reaction system (0.5 mol % [Rh(acac)(CO)$_2$], Rh/ligand = 1/10, 10 bar CO/H$_2$ = 1/1, 125 °C, Table 2, entry 5). This increase is a result of the low solubility of the olefin in the propylene carbonate phase and a deceleration of the reaction rate.[62] In addition, this approach facilitated an easy recovery of the catalyst and recycling in five runs without loss of activity or selectivity. Later, the same group used a similar rhodium catalyst system with BiphePhos **6** as ligand (Rh/ligand = 1/10) in the isomerizing hydroformylation of methyl oleate (Table 2, entry 10).[64] At a temperature of 115 °C and a pressure of 20 bar (CO/H$_2$ = 1/1), 65% of the substrate was converted, yielding only 26% of the linear $\omega$-aldehyde ester along with large amounts of hydrogenated starting material. This corresponds to a selectivity of only 40% and an average TOF of 35 $h^{-1}$. A slight increase in the aldehyde yield to 34% was observed by using ethyl linoleate which forms a conjugated system during isomerization. The authors propose a faster isomerization for this substrate compared with methyl oleate. No formation of the dialdehyde ester was observed, but large amounts of hydrogenated starting material were observed. The hydrogenation of starting material in both cases was related to the presence of the ester group of the substrate, which is considered to favor the hydrogenation pathways via $\alpha,\beta$-unsaturated esters formed through isomerization. Consequently, observed yields were much lower compared with previously reported isomerizing hydroformylation of *trans*-4-octene.

*Mechanistic Considerations on Rhodium-Catalyzed Isomerizing Hydroformylation.* The mechanistic details of the rhodium-catalyzed isomerizing hydroformylation are not known in detail to date. However, from mechanistic studies on the rhodium-catalyzed hydroformylation, in particular those dealing with the selective formation of linear aldehydes, some conclusions can be drawn.[65] The generally accepted dissociative mechanism first presented by Wilkinson and co-workers is shown in Scheme 6.[66−69]

**Scheme 6. Mechanism of Rhodium-Catalyzed Hydroformylation**



Note that the chelating phosphine shown in Scheme 6 can also be substituted by any monodentate phosphorus ligands used in (isomerizing) hydroformylation. For monodentate ligands, two isomeric forms of the catalyst can be formed, with either a diequatorial (ee) or an equatorial−apical (ea) coordination of the ligands. Contrary to that, bidentate phosphine ligands usually have a preferred mode of coordination, and therefore, one of the isomers is stabilized. Most cases of isomerizing hydroformylation use bidentate phosphine ligands; therefore, these are considered exclusively for the mechanistic argumentation.

The active species in Wilkinson's mechanism is a Rh−hydride species generated by dissociation of one CO ligand from the trigonal bipyramidal Rh−hydride complex. Coordination of the olefin substrate generates a Rh−olefin complex. Olefin insertion into the Rh−hydride and subsequent CO insertion into the Rh−alkyl species generates a Rh−acyl species that reacts with hydrogen to form the desired aldehydes and regenerates the catalytically active Rh−hydride species. Paciello and co-workers suggest that a partially irreversible olefin insertion, where the linear Rh−alkyl is irreversibly trapped and the branched Rh−alkyl can undergo β-hydride elimination to regenerate the Rh−olefin species, is responsible for the high linear selectivity.[69]

Van Leeuwen and co-workers explained the performance of their dibenzophosphindole- and diphenoxaphosphinine-substituted xanthene ligands in isomerizing hydroformylation by (a) low phosphine basicity, resulting in high isomerization and hydroformylation activity, and (b) the large natural bite angle, which induces the selectivity for linear aldehyde formation.[70] The latter is a result of the trigonal bipyramidal geometry of the rhodium complexes with bidentate phosphine ligands, which preferentially coordinate in a diequatorial mode. A large bite angle of the diphosphine ligand leads to a higher steric congestion around the metal center, especially in the apical position.[50] These crowded systems favor β-hydride elimination of branched Rh−alkyl species over CO coordination and insertion and, thus, result in higher isomerization activity, which is not the case for less congested Rh complexes. Thus, sterically congested metal centers in general favor the formation of linear aldehydes. It is important to note that in general, the overall mechanistic picture is very complex, and elementary steps are very sensitive not only to the steric and electronic effects of the phosphine ligand, but also to temperature and CO/$H_2$ pressure.[49,71,72]

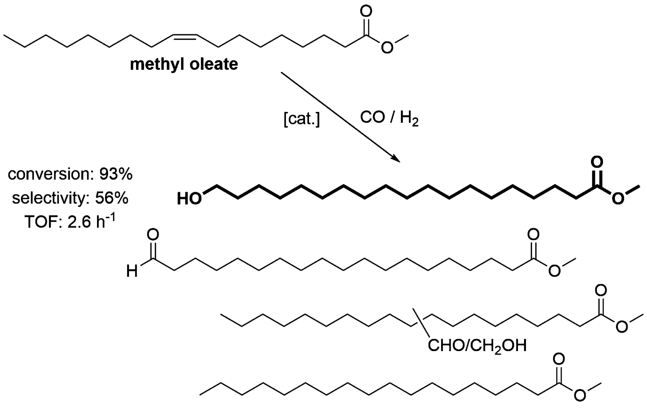
*Summary on Isomerizing Hydroformylation.* With regard to the synthesis of α,ω-functionalized compounds, by isomerizing hydroformylation, two limitations appear. The selectivity toward the linear product decreases significantly for substrates in which the double bond is in a more remote position to the terminus (1-octene >2-octene >4-octene). This is particularly important because in methyl oleate, the double bond is eight carbon atoms away, and thus, more than twice as many isomerization steps are necessary to generate a terminal olefin as compared with 4-octene. Note that catalytic productivity also decreases within this series. Hydrogenation of the substrate is a common side reaction in (isomerizing) hydroformylation. This is a problem especially for fatty acid derived substrates because α,β-unsaturated esters, which are formed through isomerization as the thermodynamically slightly favored species among the various olefin isomers (vide supra), are prone to hydrogenation, and this also results in a decreased overall selectivity to the desired ω-aldehyde ester.

## Isomerizing Hydroformylation and In Situ Reduction.

Some examples of isomerizing hydroformylation with subsequent in situ reduction of the generated aldehyde to an alcohol were reported. With regard to fatty acid esters, this would yield an ω-hydroxy ester (Scheme 7), which may be directly used, for example, as a difunctional AB-type monomer in polycondensation reactions.

In principle, two different catalyst systems are conceivable: (a) systems that catalyze both the isomerizing hydroformylation and the reduction of the formed aldehydes to an alcohol or (b) combined systems of two different catalysts, one catalyzing isomerizing hydroformylation and a second one catalyzing the reduction of the aldehyde.

**Scheme 7. Isomerizing Hydroformylation and In Situ Reduction of an Internal Olefin to the Desired ω-Hydroxy Ester and Relevant Byproducts**[a]



[a]For values of conversion, selectivity, and TOF, see ref 75.

Drent and co-workers reported the palladium/1,2-*bis*(9-phosphabicyclo[3.3.1]nonan-9-yl)ethane **7** (Figure 2, ratio = 1/1.4) catalyzed isomerizing hydroformylation and reduction,[73] generating linear alcohols from an equilibrated isomeric mixture of linear $C_8$−$C_{10}$ alkenes as the starting material (Table 3, entry 1). The desired linear alcohols were formed in a selectivity up to 72%, with a remarkably high average TOF of 1000 $h^{-1}$ at 105 °C and 60 bar ($CO/H_2$ = 1/2). Less than 1% of alkanes and ketones were noted as side products. Interestingly, formation of esters by alkoxycarbonylation of the intermediately formed Pd-acyl species with the alcohols generated during the reaction was not observed. Enhanced selectivity and productivity in the presence of substoichiometric amounts of halide anions are ascribed to a beneficial effect of the halide anion in the rate determining hydrogenolysis reaction.

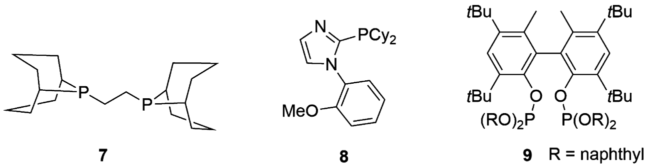


**Figure 2.** Ligands for isomerizing hydroformylation of internal olefins and reduction to terminal alcohols.

**Table 3. Isomerizing Hydroformylation and In Situ Reduction to a Terminal Alcohol**

| entry | olefin | conversion (%) | selectivity[a] (%) | TOF[b] ($h^{-1}$) | ref |
|---|---|---|---|---|---|
| 1 | $C_8$−$C_{10}$ alkenes[c] | n.a. | 72 | 1000 | 73 |
| 2 | *trans*-4-octene | 14[d] | 57 | 0.5 | 74 |
| 3 | *trans*-4-octene | 100 | 58 | 5.6 | 75 |
| 4 | methyl oleate | 86 | 43 | 2.4 | 75 |
| 5 | methyl oleate[e] | 93 | 56 | 2.6 | 75 |

[a] Selectivity toward the linear alcohol. [b] Average turnover frequencies are given, see reference for details. [c] Linear thermally equilibrated internal $C_8$−$C_{10}$ alkenes: 12% $C_8$, 44% $C_9$, 44% $C_{10}$. [d] Conversion of olefin to alcohol, no details on conversion values or side product distribution are available for this entry. [e] Addition of $Ru_3(CO)_{12}$ to catalyst system from entry 4.

The ruthenium/2-(dicyclohexylphosphino)-1-(2-methoxyphenyl)-1*H*-imidazole (**8**) catalyzed transformation of *trans*-4-octene into 1-nonanol at 160 °C, 10 bar CO, and 50 bar $H_2$ was reported by Beller and co-workers (1.2 mol % Ru, Ru/ligand = 1/2.2, Table 3, entry 2);[74] however, only a poor yield of the desired alcohol was observed (14%), with a low selectivity to the desired 1-nonanol after 24 h (this corresponds to an average TOF of 0.5 $h^{-1}$). Note that when 1-octene was used instead under slightly different reaction conditions (0.6 mol % Ru; Ru/ligand = 1/1.1; 130 °C), the alcohol yield was significantly higher (87%, along with 9% octane), with a selectivity of 92% for 1-nonanol within 20 h (this corresponds to an average TOF of 8 $h^{-1}$).

Nozaki and co-workers recently presented the synthesis of a mixture of linear alcohols and aldehydes from internal olefins (Table 3, entry 3−5) by combining a rhodium/bisphosphite **9** (ratio = 1/2; 1.0 mol % Rh) catalyst system with Shvo's ruthenium catalyst (1.5 mol %) at 120 °C and 5 bar ($CO/H_2$ = 1/1).[75] *trans*-4-Octene was converted into a mixture of alcohols and aldehydes (67%), octane (4%), and some unidentified side products (8%) (Table 3, entry 3). The observed selectivity for the linear functionalized alcohol and aldehyde mixture was 79%; the selectivity for the linear alcohol alone was only 43%. After 18 h, full conversion of the substrate was reported (this corresponds to an average TOF based on Rh of 5.6 $h^{-1}$). Note that the transformation of 1-octene under otherwise identical conditions resulted in a slightly increased selectivity (87%) to the linear functionalized product mixture, but a lower overall selectivity for the linear alcohol alone (25%).

When methyl oleate was used as the substrate, 64% of a mixture of alcohols and aldehydes along with 23% methyl stearate were formed within 36 h (this corresponds to an average TOF based on Rh of 2.4 $h^{-1}$). The selectivity to the linear $\omega$-alcohol/aldehyde ester was 48%, for the desired linear alcohol a selectivity of 43% was observed (Table 3, entry 4). The authors stated that the rate of hydroformylation was much faster than isomerization. Consequently, addition of $Ru_3(CO)_{12}$ (1.5 mol % based on Ru), which is a known precursor for alkene isomerization, resulted in an increased selectivity to the linear $\omega$-alcohol ester of 56% (Table 3, entry 5). Only trace amounts of the linear or branched aldehydes were observed; however, the amount of methyl stearate also increased to 29%.

As already observed in isomerizing hydroformylation of methyl oleate by Behr and co-workers (vide supra), the major limitation of this reaction is a low selectivity to the linear $\omega$-hydroxy ester due to hydrogenation of the substrate, which generates substantial amounts of methyl stearate.

**Isomerizing Hydroboration.** Hydroboration is typically used in organic synthesis for conversion of olefins to alkylborane species as important chemical intermediates that can easily be oxidized with alkaline hydrogen peroxide to generate hydroxy groups in an anti-Markovnikov fashion.[76,77] However, a broad range of other functional groups is also accessible. For example, alkylboranes can be transformed to carboxylates, primary or secondary amines, or alkyl bromides. In addition, C−C bond-forming reactions are possible. Among these many possibilities, oxidation to hydroxy groups is the most prominent and convenient pathway and is used in most examples of isomerizing hydroboration.

*Diborane-Initiated Isomerizing Hydroboration.* Internal alkylboranes are thermally isomerized at elevated temperatures into the respective terminal alkylboranes. The driving force for this rearrangement is the formation of the thermodynamically favored terminal alkylborane in which the boron atom is attached to the sterically least hindered position. Thus, in principle, internal olefins can be transformed into the respective terminal alcohols in high yields. Brown and co-workers observed this reaction on a mixture of decenes that was transformed into 1-decanol exclusively in 80% yield after refluxing the crude alkylborane mixture in diglyme (bp = 162 °C) for 4 h (Figure 3, reaction a).[77] Substrate, solvent, and steric effects of the substrate or the hydroboration reagent can influence the kinetics and thermodynamics of hydroboration as well as isomerization (vide infra).[78] The mechanism of the thermal isomerization remains subject to discussion. Theoretical studies indicate that dehydroboration followed by olefin readdition, as already proposed by Brown and co-workers, is most likely.[79]

With regard to unsaturated fatty acids, isomerizing hydroboration with subsequent oxidation generating a terminal hydroxy group would be of interest as a route to unsymmetric $\alpha,\omega$-functionalized compounds (Scheme 8); however, when methyl oleate was used instead of a nonfunctionalized olefin under the aforementioned reaction conditions, thermal isomer-

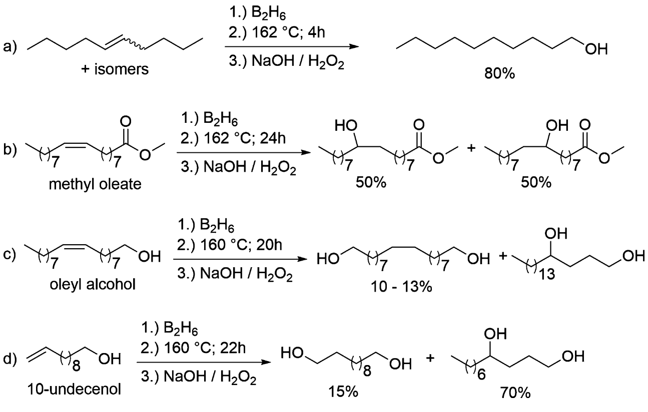
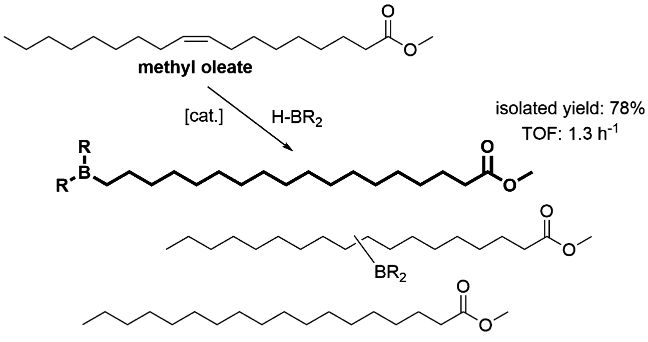


**Figure 3.** Hydroboration, thermal isomerization and oxidation with NaOH/$H_2O_2$ of decene (a),[77] methyl oleate (b),[80] oleyl alcohol (c),[81] and 10-undecenol (d)[82] with diborane ($B_2H_6$).

ization to the linear $\alpha,\omega$-functionalized product was not observed. Even after prolonged exposure to the typical conditions, only the respective 9- and 10-hydroxyoctadecanoic acids were obtained (Figure 3, reaction b).[80]

**Scheme 8. Isomerizing Hydroboration of Methyl Oleate to the Desired $\omega$-Boran Ester and Relevant Byproducts[a]**



[a]For values of isolated yield and TOF, see ref 101.

In another study, oleyl alcohol was used instead of methyl oleate. Employing isomerization times of up to 20 h resulted in 10−13% of the desired 1,18-octadecanediol (Figure 3, reaction c). Furthermore, a significant amount of 1,4-octadecanediol was identified, which indicates that thermal migration of the boron atom occurs in both directions, as expected; however, it may be trapped in the 4-position of the hydrocarbon chain due to formation of a six-membered ring by coordination of the oxygen atom of the terminal hydroxyl group to the boron atom.[81] This was also observed in hydroboration of 10-undecenol forming 1,11- and 1,4-undecanediol as the main products. Thermal isomerization at 160 °C for 3 h and subsequent oxidation yielded 56% 1,4-undecanediol and 40% 1,11-undecanediol. This amount increased to 70% 1,4-undecanediol after 22 h of isomerization time prior to oxidation. A yield of 15% 1,11-undecanediol was noted under these reaction conditions (Figure 3, reaction d).[82] These observations indicate that in the presence of functional groups, such as an alcohol functionality, isomerization to the terminal alkylborane is hindered, and the product distribution is altered significantly, as compared with nonfunctionalized olefins.

*Metal-Catalyzed Isomerizing Hydroboration.* The aforementioned reactions used diborane as a hydroboration reagent. More recent approaches employed sterically demanding 4,5-substituted 1,3,2-dioxaborolanes (e.g., catecholborane or pinacolborane), which are easier to handle and exhibit a better thermal stability; however, their reactivity is generally lower compared with diborane because the attachment of the boron atom to a heteroatom, such as oxygen, possibly lowers the Lewis acidity of the boron atom.[83] Thus, transition metal catalysis is used to accelerate these hydroborations as first described by Männig and Nöth.[84] Moreover, these catalyzed hydroborations allow for better control of chemo-, regio-, and stereoselectivity.[84−86] Within this review, systems that undergo isomerizing hydroboration will be addressed exclusively because these potentially allow for the preparation of $\alpha,\omega$-functionalized compounds from unsaturated fatty acids.

*Rhodium-Based Catalysts.* Several rhodium-catalyzed isomerizing hydroborations of internal olefins have been reported.

Srebnik and co-workers studied the isomerizing hydroboration of *trans*-4-octene with pinacolborane, resulting in an isolated yield of 92% of the linear 1-octyl-pinacolborane exclusively, by 1 mol % [$Rh(PPh_3)_3Cl$] (Wilkinson's catalyst) within 10 min at 25 °C (this corresponds to an average TOF of 552 $h^{-1}$, Table 4, entry 1).[87] The same group also reported that by using [$Rh(CO)(PPh_3)_2Cl$] instead of Wilkinson's catalyst, the respective 4-octyl-pinacolborane was obtained in a high selectivity of 97% and only 3% of the desired linear 1-octyl-pinacolborane (in 94% overall yield).[88]

**Table 4. Rhodium-Catalyzed Hydroboration of Internal Octenes with Pinacolborane**

| entry | olefin | yield[a] (%) | linear selectivity[b] (%) | TOF[c] ($h^{-1}$) | ref |
|---|---|---|---|---|---|
| 1 | *trans*-4-octene | 92 | 100 | 552 | 87 |
| 2 | *trans*-4-octene | 72 | 100 | 0.8 | 92 |
| 3 | *trans*-4-octene[d] | 73 | 100 | 110 | 92 |
| 4 | 1-, 2-, 4-octene[e] | 85[f] | 100 | n.a. | 93 |

[a]Yield of octyl-pinacolborane. [b]Selectivity toward the linear product. [c]Average turnover frequencies are given; see reference for details. [d]Acceleration of reaction compared with entry 2 (identical reaction conditions) by microwave irradiation. [e]Equimolar mixture or 1-, 2-, and 4-octene. [f]Yield of 1-nonanal, n.a. = not available.

These findings stand in contrast to earlier work by Evans and co-workers, who performed mechanistic studies on rhodium(I)-catalyzed hydroboration. Applying freshly prepared Wilkinson's catalyst and catecholborane in hydroboration of 1-olefins resulted in highly selective formation of the linear product; however, if 4-octene was used as a substrate, formation of 4-octyl-catecholborane was observed exclusively.[89] These observations may lead to the conclusion that the hydroboration reagent itself (namely, its steric congestion) influences the chemoselectivity of the reaction.[90] However, subsequently, Miyaura et al.,[91] Robinson et al.,[92] and Crudden et al.[93] among others failed to reproduce Srebnik's results. This can possibly be accounted for by a beneficial effect of oxygen inadvertently present, which induces isomerizing hydroboration because both Robinson[92] and Crudden[93] observed enhanced catalytic activity in the presence of oxygen. Note that oxygen treatment of Wilkinson's catalysts results in the formation of the oxygen-coordinated rhodium species [$RhO_2(PPh_3)_2Cl$]$_2$ and [$RhO_2(PPh_3)_3Cl$], respectively.[94−96]

Robinson and co-workers observed isomerizing hydroboration of *trans*-4-octene with pinacolborane to the linear

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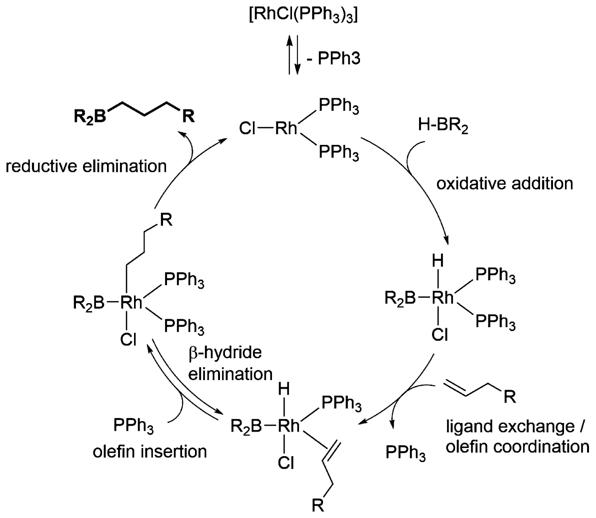
*ACS Catal.* 2015, 5, 5951−5972

octyl-pinacolborane in 72% yield (by $^{11}B$ NMR spectroscopy) within 48 h at 25 °C in the presence of 2 mol % oxygen treated Wilkinson's catalyst (this corresponds to an average TOF of 0.8 $h^{-1}$, Table 4, entry 2).[92] A significant acceleration of the transformation was observed by microwave irradiation at 25 °C, resulting in a 73% yield of the linear octyl-pinacolborane already after 20 min (this corresponds to an average TOF of 110 $h^{-1}$, Table 4, entry 3).[92] Crudden and co-workers observed that the application of catalyst precursors with a decreased phosphine to rhodium ratio (e.g., $[Rh(PPh_3)_2Cl]_2$ or $[Rh(C_2H_4)_2Cl]_2$ with 1.25 equiv. $PPh_3$) resulted in an enhanced catalytic activity in hydroboration of 1-octene with pinacolborane.[93] This approach also enabled the transformation of an equimolar mixture of 1-, 2-, and 4-octene with $[Rh(C_2H_4)Cl]_2$ and 1.25 equiv of $PPh_3$ to the respective linear 1-octyl-pinacolborane within a one-pot transformation to 1-nonanal in an overall yield >85% (Table 4, entry 4).

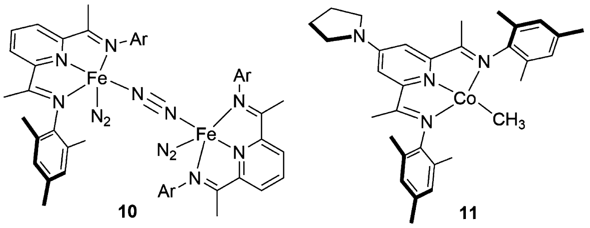
In the generally accepted mechanism of rhodium-catalyzed hydroboration suggested by Männig and Nöth (Scheme 9),[84] dissociation of the triphenylphosphine ligand is necessary prior to oxidative addition of the H−$BR_2$ species. Thus, the observation of a reduced phosphine-to-rhodium ratio enhancing the catalytic activity is in line with this mechanistic feature. Isomerization of the olefin with a rhodium species is ascribed to proceed via an olefin insertion/β-hydride elimination mechanism-catalyzed by the rhodium hydride species that is formed by oxidative addition of the hydroboration reagent to the metal center.[84,86,97] Consequently, isomerization of internal olefins into a mixture of all isomers is observed, as expected.[94] In their mechanistic study on the hydroboration of 1-decene and 2-octene, Evans and co-workers suggested that olefin insertion into the Rh−hydride is, indeed, reversible but sensitive to the steric bias around the metal center.[89]

**Scheme 9. Proposed Mechanism of Catalytic Hydroboration by Männig and Nöth[84]**



Summing up all the above-mentioned observations, one may conclude that low phosphine concentrations and oxygen coordination to the rhodium(I) species (vide supra) can form a catalytic system that facilitates isomerizing hydroboration on internal olefins. This isomerizing hydroboration tandem approach can be accounted for by the accepted mechanism for hydroboration reactions. However, concerning the scope of this review, it is important to note that to the best of our knowledge, rhodium-catalyzed isomerizing hydroboration of fatty-acid-derived substrates has thus far not been reported.

*Cobalt- and Iron-Based Catalysts.* Recently, Chirik and co-workers reported the bis(imino)pyridine cobalt[98] and bis(imino)pyridine iron[99]-catalyzed isomerizing hydroboration of internal olefins using pinacolborane as a hydroboration agent (Figure 4).



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11

**Figure 4.** Iron- and cobalt-based catalyst precursors for isomerizing hydroboration of internal olefins.

More than 98% conversion of *cis*-4-octene to the linear octyl-pinacolborane was observed in the presence of 1 mol % of iron catalyst precursor **10** within 24 h at 25 °C (corresponding to an average TOF of 4.1 $h^{-1}$).[99] However, in the presence of a carbonyl group in the substrate (*trans*-pent-3-en-2-one), no productive hydroboration was observed, indicating that carbonyl groups inhibit catalysis.

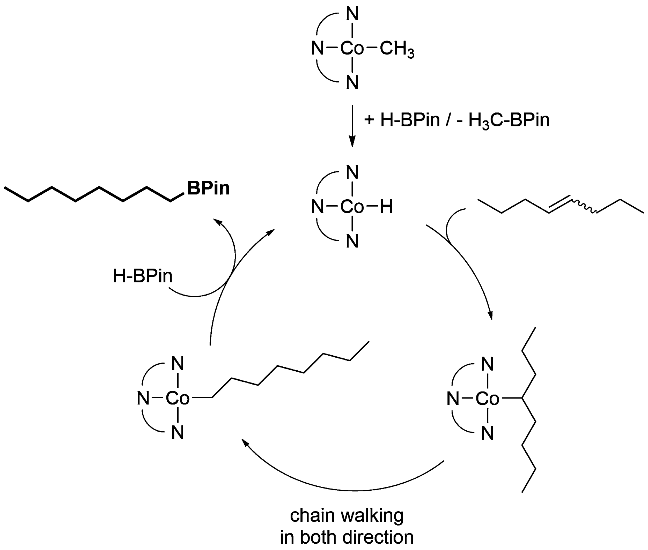
With the cobalt-based catalyst precursor **11**, >98% conversion of *cis*- and *trans*-4-octene to the linear octyl-pinacolborane was observed in the presence of 1 mol % of catalyst within 1.5 h at 23 °C (this corresponds to an average TOF of 65 $h^{-1}$).[98] When methyl 3-hexenoate was used as the substrate, the conversion was 88% with a selectivity of 70% to the linear alkyl-pinacolborane (GC-FID) after 24 h at 23 °C (this corresponds to an average TOF of 3.7 $h^{-1}$). Although the catalytic activity is significantly altered in the presence of an ester group, this study shows that conversion of unsaturated esters to the respective linear α,ω-functionalized compound via cobalt-catalyzed hydroboration is feasible.

From deuterium labeling experiments, a mechanism involving a Co−hydride as the catalytically active species, which is formed by reaction of pinacolborane with the Co−methyl precursor, is proposed. Insertion of the internal olefin into the Co−hydride results in the formation of a secondary alkyl species, which then undergoes isomerization by a sequence of β-hydride eliminations and reinsertions until a terminal Co−alkyl species is formed. This terminal species reacts with pinacolborane to regenerate the catalytically active Co−hydride species and results in the formation of the desired linear alkylborane (Scheme 10). Because conversion of 1-octene was faster than conversion of 4-octene, the authors concluded that isomerization is the rate-limiting step in this transformation.

*Iridium-Based Catalysts.* Miyaura and co-workers reported the iridium(I)-catalyzed isomerizing hydroboration of *cis*- and *trans*-4-octene with pinacolborane in the presence of 1.5 mol % $[Ir(COD)Cl]_2$ with 3 mol % dppm, yielding 78% of the linear octyl-pinacolborane after 24 h at 25 °C (this corresponds to an average TOF of 1.1 $h^{-1}$).[91]

Two reports address the iridium-catalyzed isomerizing hydroboration of unsaturated fatty acids. Angelici and co-workers used 3.3 mol % $[Ir(COE)_2Cl]_2$ with 6.6 mol % dppe as

**Scheme 10. Proposed Mechanism of Bis(imino)pyridine Cobalt (11)-Catalyzed Isomerizing Hydroboration**[98]

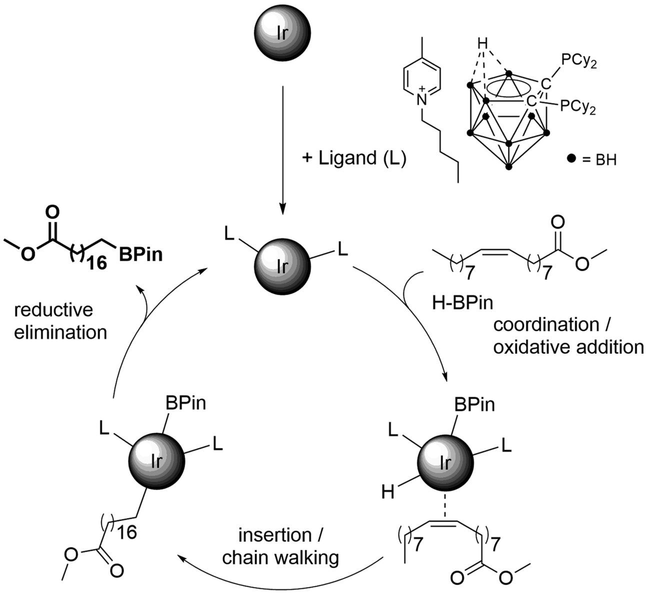


a catalyst precursor for the hydroboration of methyl oleate and obtained the terminal boronate ester in 45% yield (GC-MS), along with 8% nonidentified isomers and 47% hydrogenation product methyl stearate after 24 h at 25 °C (corresponding to an average TOF of 1.3 $h^{-1}$).[100] Note that isomerizing hydroboration of methyl 10-undecenoate under identical conditions yielded 92% of the desired linear boronate ester with only 8% hydrogenated byproduct. The authors proposed an iridium-catalyzed isomerization with subsequent iridium-catalyzed hydroboration of the terminal olefin as the operative catalytic mechanism. Iridium-catalyzed hydroboration of methyl oleate in the 9- or 10-position and subsequent thermal isomerization to the terminal boronate ester seems unlikely, since tris(carbomethoxyalkyl)boranes (with the boron atom at the 9- or 10-position) do not undergo isomerization, as already shown by Bickford and co-workers.[80]

A more recent study by Zhu and co-workers reported the use of iridium nanoparticles (2.5 mol %) in the presence of 6.6 mol % 1,2-bis(dicyclohexylphosphino)-1,2-dicarba-*closo*-dodecaborane as diphosphine ligand in an ionic liquid/methylene chloride mixture for isomerizing hydroboration of methyl oleate with pinacolborane. After 24 h at 25 °C, 78% of the linear hydroboration product was isolated (this corresponds to an average TOF of 1.3 $h^{-1}$).[101] The authors stated that no hydrogenated starting material was observed. Isomerizing hydroboration of methyl 10-undecenoate under the same conditions yielded 96% of the desired linear product. When $[Ir(COE)_2Cl]_2$ was used instead of the Ir nanoparticles for hydroboration of methyl oleate, the yield was significantly lower (55%) under otherwise identical conditions. Mercury-poisoning studies showed evidence for heterogeneous catalysis. A mechanism was proposed in which the diphosphine coordinates to the iridium nanoparticles, which then activates the B–H bond of pinacolborane and generates an Ir–hydride on the particles' surface. Oleate can insert into the Ir–hydride and isomerizes to the terminal Ir–alkyl species. Reductive elimination results in formation of the desired linear alkylborane (Scheme 11).

In summary, isomerizing hydroboration is very effective for generation of linear functionalized compounds from nonfunctionalized olefins, but only a few reports of isomerizing hydroboration of unsaturated esters exist. Both selectivity and productivity of these systems are rather low as compared with other isomerizing functionalization approaches.

**Scheme 11. Proposed Mechanism of Iridium-Nanoparticle-Catalyzed Isomerizing Hydroboration**[101]



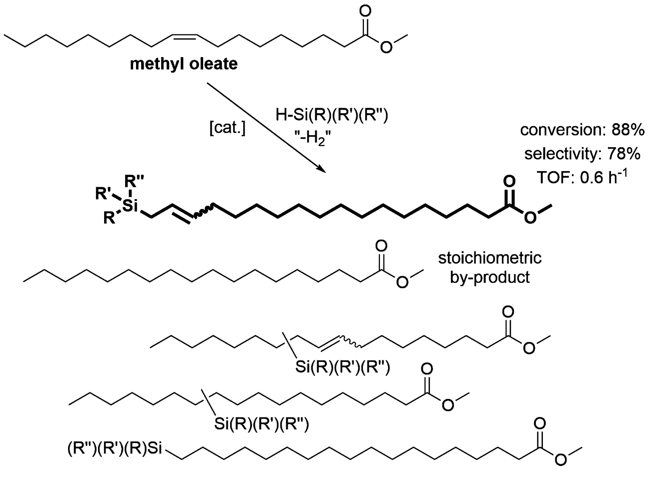
**Isomerizing Silylation.** Among the various known silylation reactions, the isomerizing dehydrogenative silylation and isomerizing hydrosilylation are of interest because these potentially allow for ω-functionalization of fatty acids.

Isomerizing dehydrogenative silylation aims at producing a terminal carbon–silicon bond starting from an olefin and a silicon hydride species H–Si(R)(R′)(R″), maintaining the double bond of the molecule (Scheme 12). Thus, part of the olefin is hydrogenated, or addition of a sacrificial olefin as a hydrogen scavenger is necessary. Isomerizing hydrosilylation also aims at producing a terminal carbon–silicon bond from the same starting materials; however, the silicon hydride inserts formally into the olefinic double bond (Scheme 13). Thus, hydrogenation is not a stoichiometric side reaction or addition of sacrificial olefins is not necessary.

Generally, silylation reactions are strongly influenced by the nature of the silicon hydride and the olefinic substrate. The addition of silicon hydrides to olefinic double bonds can be catalyzed by radicals (e.g., peroxide or azo compounds) or by a large variety of transition metal catalysts (e.g., Fe, Co, Rh, Ir, Pd, Pt, Ru). Transition metal catalysis appears more relevant here in view of the fact that an isomerization step, that can be brought about by the transition metal, is necessary prior to silylation. Several mechanisms have been proposed for the metal-catalyzed transformations, differing for each ligand–metal system. Here, we focus on selected examples of isomerizing silylation that appear potentially interesting for ω-functionalization of fatty acids.

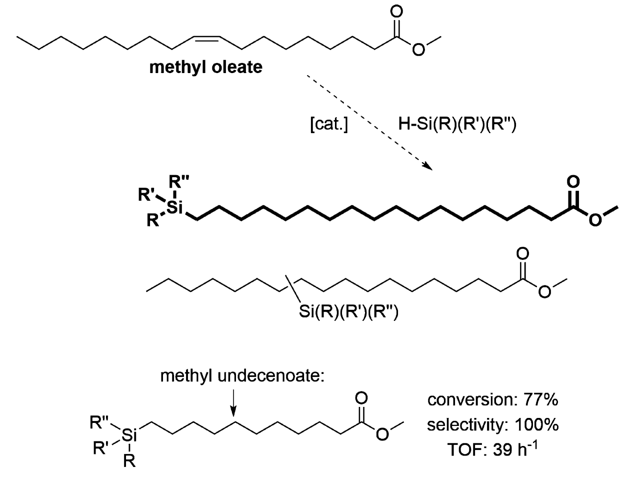
Early on, Speier and co-workers reported hydrosilylation of 1- and 2-pentene with $H{-}SiMeCl_2$ in the presence of platinum ($H_2PtCl_6$, $K_2PtCl_4$, Pt/C) or ruthenium ($RuCl_3$) catalysts, yielding the respective linear 1-pentylsilane from either substrate.[102] When a peroxide initiator was used instead of the aforementioned metal species (note that $H{-}SiCl_3$ was used as the silicon hydride in this case), the formation of the expected 2- and 3-pentylsilanes was observed.[103] Speier and co-

**Scheme 12. Isomerizing Dehydrogenative Silylation of Methyl Oleate to the Desired ω-Allylsilyl Ester and Possible Byproducts**[a]



[a]For values of conversion, selectivity, and TOF see ref 111.

**Scheme 13. Isomerizing Hydrosilylation of Methyl Oleate to the Desired ω-Silyl Ester and Possible Byproducts**[a]

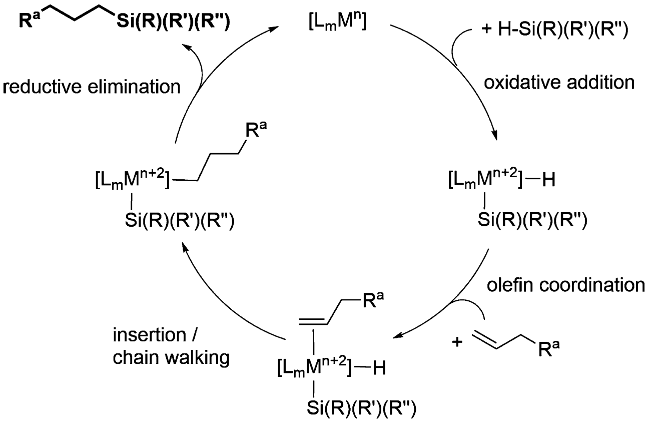


[a]For values of conversion, selectivity and TOF see ref 110.

workers later reported the formation of linear 1-heptylsilanes from 3-heptene and H$-$SiCl$_3$, H$-$SiMeCl$_2$, and H$-$SiMe$_2$Cl in the presence of catalytic amounts of $H_2PtCl_6$ with excellent yields (92%, 93%, 61%, respectively).[104] As a mechanism, a metal-assisted hydride donation to the double bond of the substrate was proposed, forming an internal 3- or 4-carbanion that isomerizes into the more stable terminal 1-carbanion, which then forms the linear 1-heptylsilane by nucleophilic attack on the silicon atom.

Chalk and Harrod proposed a mechanism for the homogeneously catalyzed hydrosilylation reaction based on studies with iridium and platinum complexes (Scheme 14).[105] Oxidative addition of the silane results in the formation of a metal hydride species. The olefin coordinates to the metal center and is inserted into the metal hydride bond, yielding a metal alkyl species. Reductive elimination results in regeneration of the catalytically active species and in formation of the hydrosilylation product. This mechanism also accounts for the formation of terminal 1-alkylsilanes from internal olefins, if olefin insertion into the metal hydride species is reversible. This was also pointed out by Chalk and Harrod, who proposed isomerizing silylation if β-hydride elimination is faster than reductive elimination.

**Scheme 14. Chalk-Harrod Mechanism for the Metal-Catalyzed Hydrosilylation of Olefins**[105]



Chirik and co-workers recently presented the bis(imino)-pyridine cobalt-catalyzed isomerizing dehydrogenative silylation of 4-octene, producing exclusively the linear (1-octenyl)silane in addition to stoichiometric amounts of octane (Table 5, entry 1).[106] By stirring a mixture of *cis*- or *trans*-4-octene and H$-$SiMe(OSiMe$_3$)$_2$ in the presence of 1 mol % of the cobalt catalyst precursor for 24 h at 23 °C, quantitative formation of the terminal allylsilane and stoichiometric amounts of octane were observed (this corresponds to an average TOF of 4.2 $h^{-1}$). Note that when 1-octene was used as a starting material, the reaction was significantly faster, and full conversion was observed within 15 min (this corresponds to an average TOF of 800 $h^{-1}$). By monitoring the progress of the silylation of 4-octene, 2- and 3-octene isomers were noted as intermediates. From this and other investigations, Chirik et al. proposed a mechanism (Scheme 15) in which the catalytically active Co$-$silyl species inserts the terminal olefin into a 2,1-insertion and generates a Co$-$alkyl species, which undergoes β-hydride elimination to form the terminal allylsilane, and a Co$-$hydride species. According to the authors, β-hydride elimination is preferred on the carbon atom away from the large tertiary silane substituent, thus resulting in the selective formation of allylsilanes. The Co$-$hydride is responsible for isomerization of the 4-octene substrate into a mixture of 1-, 2-, 3-, and 4-octene and thus brings about isomerizing silylation. Reaction of a Co$-$alkyl species with a silane (σ-bond metathesis) to regenerate the Co$-$silyl and to generate the respective alkane is the rate-limiting step.

Speier and co-workers already reported the hydrosilylation of methyl oleate with H$-$SiPh$_3$ by using 10 mol % of *tert*-butyl peroxybenzoate.[107] After 18 h at 90 °C, quantitative conversion to the hydrosilylation product was observed; however, the authors did not comment on the position of the $-$SiPh$_3$ group.

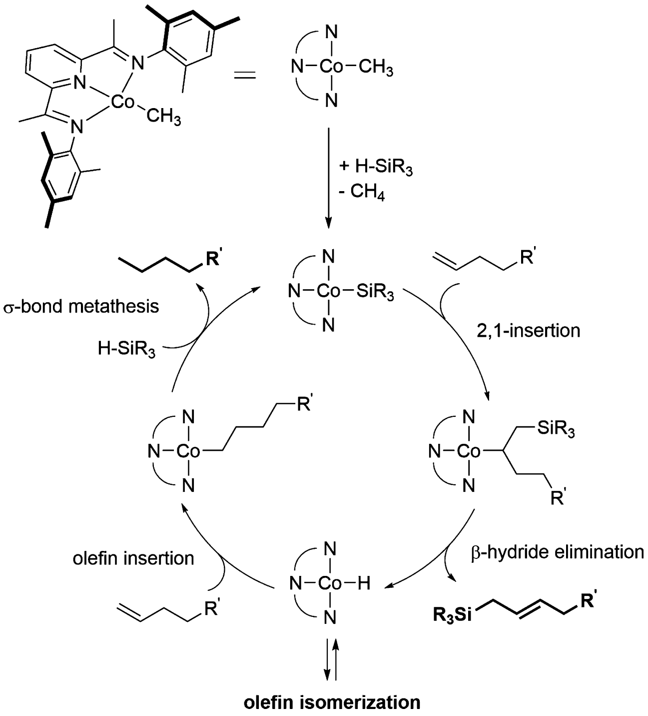
The platinum-catalyzed hydrosilylation of methyl 10-undecenoate and methyl oleate using different silanes (among others: H$-$SiCl$_3$, H$-$SiMeCl$_2$, H$-$Me$_2$Cl, and H$-$SiPhCl$_2$) was reported by Gertner and co-workers (Table 5, entry 2).[108] Hydrosilylation of methyl undecenoate yielded 97% of the desired linear product at 90 °C after 5 h with only 0.01 mol % of $H_2PtCl_6$. For methyl oleate, a higher catalyst loading was necessary (0.1 mol %) to reach a conversion of 75% under

**Table 5. Isomerizing Dehydrogenative Silylation (entries 1, 5) and Hydrosilylation (entries 2–4) of Various Substrates**

| entry | olefin | conversion (%) | selectivity[a] (%) | TOF[b] ($h^{-1}$) | ref |
|---|---|---|---|---|---|
| 1 | 4-octene[c] | >98 | 50 | 4.2 | 106 |
| 2 | methyl undecenoate[d] | 97 | 100 | 20 | 108 |
| 3 | methyl undecenoate[e] | 92 | 45 | 46 | 110 |
| 4 | methyl undecenoate[f] | 77 | 100 | 39 | 110 |
| 5 | methyl oleate[g] | 88 | 78 | 0.6 | 111 |

[a] Selectivity toward the linear product. [b] Average turnover frequencies are given; see reference for details. [c] A 2:1 mixture of *cis-* and *trans-*4-octene was used for Co-catalyzed silylation with $H{-}SiMe(OSiMe_3)_2$. [d] 2 equiv of $H{-}SiMeCl_2$, 0.01 mol % $H_2PtCl_6$, 90 °C, 5 h. [e] Stoichiometric amounts of $H{-}SiMeCl_2$, 1 mol % $H_2PtCl_6$, 40 °C, 2h. [f] Stoichiometric amounts of $H{-}Si(OEt)_3$, 1 mol % $H_2PtCl_6$, 40 °C, 2h. [g] 3 equiv of $H{-}Si(Et)_3$, 8 mol % $[Ir(OMe)(COD)]_2$, 3 equiv of norbornene, 60 °C, 24 h.

**Scheme 15. Proposed Mechanism of Isomerizing Dehydrogenative Silylation of 4-Octene to Linear Allylsilane[106]**



otherwise identical conditions; however, only internal hydrosilylation products were observed; the exact position of the silyl moiety was not reported. Rivière and co-workers confirmed these results on hydrosilylation of 10-undecenoate and methyl oleate in an almost identical study.[109] The authors also reported that Wilkinson's catalyst is suitable for the silylation of methyl 10-undecenoate, albeit it is less efficient (conversion of 72% at 120 °C in 24 h with $H{-}SiMeCl_2$). Behr and co-workers investigated the hydrosilylation of methyl 10-undecenoate and ethyl oleate in a biphasic cyclohexane/propylene carbonate system (Table 5, entry 3, 4).[110] With 1 mol % $H_2PtCl_6$, the linear hydrosilylation product of methyl 10-undecenoate was formed with a selectivity of 45% for $H{-}SiMeCl_2$ (entry 3) and 100% for $H{-}SiOEt_3$ (entry 4), respectively. For ethyl oleate, no formation of the hydrosilylation products was observed.

The first and, to the best of our knowledge, only isomerizing silylation of unsaturated fatty acids was reported by Riepl and co-workers (Table 5, entry 5).[111] For the isomerizing dehydrogenative silylation of methyl oleate 8 mol % of $[Ir(OMe)(COD)]_2$ as a catalyst precursor, 3 equiv of $H{-}SiEt_3$, and 3 equiv of norbornene as a sacrificial substrate were used. After 24 h at 60 °C, the conversion of methyl oleate was 88% with a selectivity of 78% for the desired linear dehydrogenative silylation product (this corresponds to an average TOF of 0.6 $h^{-1}$). As side reactions, hydrogenation of methyl oleate (6% yield) and the formation of internally silylated products (8% yield) were observed, along with other unidentified products. The authors did not comment on the mechanism of this transformation. On the basis of the results, one could conclude that silyl migration and subsequent β-hydride elimination are necessary to account for the formation of unsaturated products. Assuming that oxidative addition of carbon–silicon bonds to the metal center is not possible and σ-bond metathesis is irreversible, there are still several possible pathways that may generate the linear α,ω-functionalized fatty acid derivative such that no final conclusion on the selectivity-determining step can be drawn.

It is important to note that the reactivity and, thus, the potential application of the alkyl-Si(R)(R′)(R″) species generated by isomerizing silylation are strongly dependent on the nature of the substituents R, R′, and R″. For example, from alkyl–silyl chlorides, the respective silanoles, siloxides, or silyl ethers can be generated, which may be used as additives in polycondensation reactions to generate silicons.

**Isomerizing Alkoxycarbonylation.** Alkoxycarbonylation is a well-known and mechanistically well-understood reaction.[38,112–122] Methoxycarbonylation of ethylene with CO and methanol to methyl propionate has recently been commercialized as part of a novel process for methyl methacrylate production.[123,124] This reaction is catalyzed with high rates by palladium(II) complexes of 1,2-$(CH_2P^tBu_2)_2C_6H_4$ (dtbpx, **12**, Figure 5).[125]

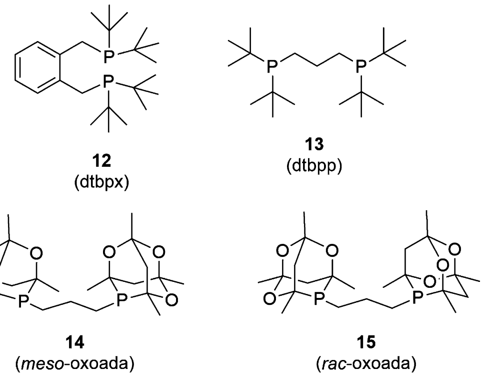


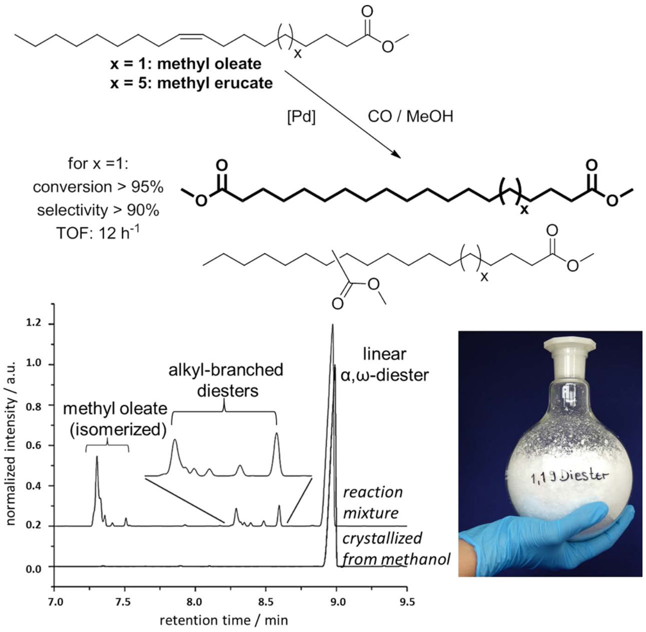
**Figure 5.** Diphosphane ligands for isomerizing alkoxycarbonylation.

Pringle and co-workers reported that palladium(II) complexes modified with *meso*/*rac* 1,3-bis(phospha-oxa-adamantyl)-propane (*meso*/*rac*-oxoada **14**/**15**, Figure 5) or 1,3-bis(di-*tert*-butylphosphino)propane (dtbpp, **13**, Figure 5) convert the double bond of internal olefins to a terminal ester group with high selectivity.[126] From a thermodynamically equilibrated mixture of linear $C_{14}$-olefins (<0.2% terminal olefin), the formation of the linear, terminally functionalized methyl 1-pentadecanoate was observed with a selectivity of 78% (**14**/**15**) and 75% (**13**), respectively, at 115 °C and 30 bar CO. Average TOFs were 120 $h^{-1}$ for *meso*/*rac*-oxoada (**14**/**15**) and 5 $h^{-1}$ for dtbpp (**13**). Cole-Hamilton and co-workers later reported the transformation of 4-octene to the linear, terminally functionalized methyl 1-nonanoate in 94% selectivity by a palladium(II) catalyst modified with the aforementioned diphosphine dtbpx (**12**) at 80 °C and 30 bar CO with an average TOF of 4 $h^{-1}$ (note that the conversion was 100%; thus, this TOF may be underestimated).[127] In their study, Cole-Hamilton and co-workers concluded that in isomerizing methoxycarbonylation of internal olefins, a hydride mechanism is operative, and methanolysis is the rate-determining step. Both studies used an in situ catalyst system consisting of a Pd source with excess diphosphine and methanesulfonic acid. As the Pd source, Pringle used [$Pd(OAc)_2$] (ratio olefin/Pd/diphosphine/acid = 700/1/1.5/2.5), and Cole-Hamilton used [$Pd_2(dba)_3$] (ratio olefin/Pd/diphosphine/acid = 62.5/1/2.5/5).

Cole-Hamilton and co-workers also reported a first example of the isomerizing methoxycarbonylation of methyl oleate (Scheme 16) using a catalyst system similar to that previously reported for isomerizing methoxycarbonylation of 4-octene (ratio olefin/Pd/diphosphine/acid = 62.5/1/5/10).[128] Methyl oleate was converted into the respective linear *α*,*ω*-diester dimethyl 1,19-nonadecanedioate in high selectivity at 40 °C and 20 bar CO, as observed by gas chromatography. Surprisingly, this remarkable finding did not receive further attention at the time. We refined this approach to generate and isolate linear long-chain *α*,*ω*-diesters from oleates and erucates on a preparative scale, which were then used to generate polyesters.[12] These in situ catalyst approaches always use an excess of the relatively expensive diphosphine dtbpx. This issue was overcome by using [$(dtbpx)Pd(OTf)_2$] as a single component defined catalyst precursor.[13] This precursor not only eliminates the necessity of excess diphosphine, but moreover, the catalytic productivity is 30−50% higher (based on Pd) as compared with the in situ system with virtually identical selectivity (around 90%) to the linear *α*,*ω*-diesters. An analysis of the byproducts formed showed that all conceivable alkyl-branched diesters are formed in very small amounts, with the methyl-branched diester as the major byproduct (yield by GC: 3.5%, retention time 8.7 min in Scheme 16).[129] Thus, alkoxycarbonylation occurs in all positions of the fatty acid chain, but with a very high terminal selectivity. The desired linear *α*,*ω*-diester can be obtained in polycondensation purity (>99%) by simple crystallization from the reaction mixture (Scheme 16).

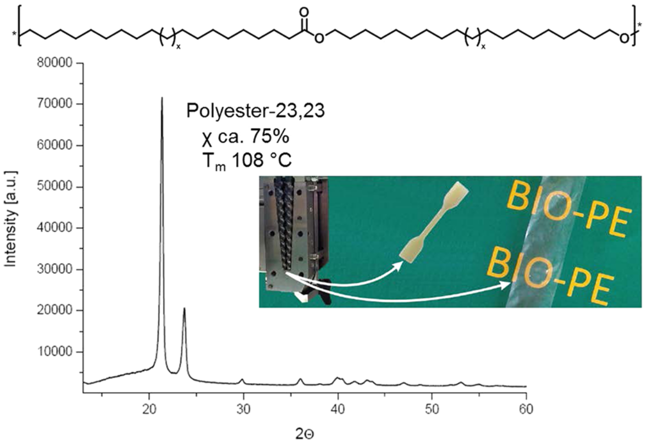
The linear *α*,*ω*-diester can be further reduced to the diol, which then enables polycondensation of these two compounds to semicrystalline polyesters.[12] The incorporation of the long-chain hydrocarbon segments derived from the fatty acids results in high crystallinities, which becomes obvious from the WAXS pattern of the polyester-23,23 (poly[1,23-tricosadiyl-1,23-tricosanedioate]) generated from erucic acid. The crystalline properties of the plant-oil-based polyesters are "polyethylene-like" in the sense of an essentially similar solid state structure. In addition, these polyesters show a high melting temperature (>100 °C) comparable to the thermal properties of typical thermoplastics (Scheme 17). Moreover, these plant-oil-based polyesters are easily processable and meet the requirements of injection molding, film extrusion, and electrospinning.[12,16] Beyond that, the *α*,*ω*-diester and further functionalizations (e.g., to diols or diamines) allow for the generation of polyamides, polyacetals, and polycarbonates from plant oils.[13,17,18]

**Scheme 16. Palladium-Catalyzed Isomerizing Methoxycarbonylation of Methyl Oleate and Methyl Erucate (top), GC Trace of Crude Reaction Mixture with Side Product Distribution and Purified 1,19-Diester from Methyl Oleate (>99%) Catalyzed by [$(dtbpx)Pd(OTf)_2$] (bottom)[a]**



[a]For values of conversion, selectivity and TOF see refs 129 and 134.

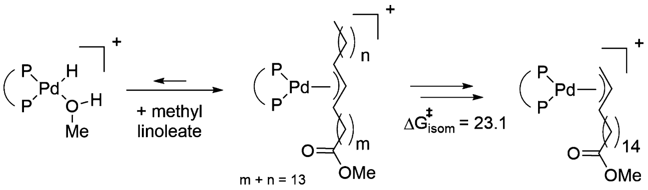
**Scheme 17. Polyester-23,23 from Erucic Acid, WAXS Pattern of Polyester-23,23 and Photograph of Tensile Testing Bars and Films from Injection Molding and Melt Extrusion[12,16]**



It is important to note that both the in situ catalyst system and the defined catalyst precursor are not only capable of transforming pure oleate but also commercially available technical grade plant oils that are mixtures of fatty acids with different numbers of carbon atoms and, in particular, multiple double bonds (cf. Table 1).[12,21,128,130−133] Linoleate, as a major component of tall oil, is also converted to the linear *α*,*ω*-diester 1,19-nonadecenedioate, although only with a significantly decreased selectivity of 45% for the linear diester with the defined catalyst precursor.[21,132,134] Whereas the reaction of methyl oleate (or high oleic sunflower oil) proceeds with a selectivity of >90% and an average TOF of 12 $h^{-1}$ to the saturated *α*,*ω*-diester, the conversion of methyl linoleate under identical conditions is less selective and with an average TOF of only 2 $h^{-1}$ to the monounsaturated *α*,*ω*-diester.

This significant decrease in the reaction rate is a result of the formation of a stable, disubstituted internal Pd−allyl species that isomerizes to the monosubstituted terminal Pd−allyl species (Scheme 18), from which carbonylation occurs.[134] Energetic barriers for the isomerization with this Pd−allyl species are significantly increased compared with methyl oleate and the respective Pd−alkyl species. In combination with the decreased reaction rate, which leaves more time for other reaction pathways to occur, the presence of a second double bond in linoleate allows a range of side reactions, which lowers the selectivity toward the desired linear *α*,*ω*-diester.

**Scheme 18. Formation of the Pd−Allyl Species with Stoichiometric Amounts of Catalytically Active Pd−Hydride Species $[(\mathrm{dtbpx})\mathrm{PdH}(\mathrm{CH_3OH})]^+$ and Isomerization to the Terminal Pd−Allyl Species (ΔG in kcal $mol^{-1}$)[134]**

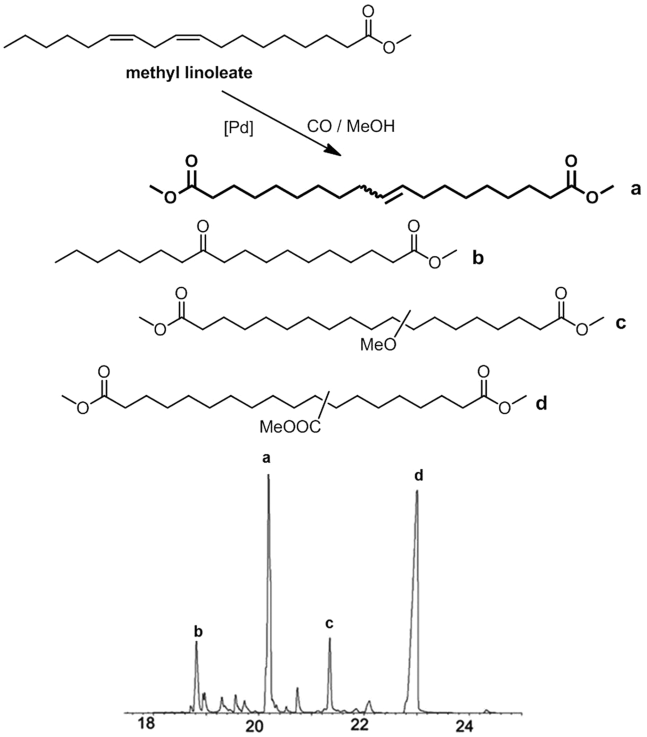


Cole-Hamilton and co-workers were able to identify the products formed in this reaction catalyzed by the in situ Pd−catalyst generated from $[\mathrm{Pd_2(dba)_3}]$ with dtbpx and methanesulfonic acid (MSA) in methanol at 30 bar CO and 90 °C over 48 h (Scheme 19).[132]

The major product was the linear, monounsaturated *α*,*ω*-diester (**a**) with the remaining double bond at different positions along the chain. This compound is easily hydrogenated to the saturated *α*,*ω*-diester. Other components identified were the $C_{18}$ keto ester (**b**), the methoxy-substituted diester (**c**) resulting from mono alkoxycarbonylation and hydromethoxylation of the remaining double bond, and the triester (**d**) formed by double alkoxycarbonylation of linoleate. Note that each compound is a mixture of isomers with the third functionality distributed over all positions along the chain. During our own investigations on the fate of multiple unsaturated fatty acids during isomerizing methoxycarbonylation formation of a terminal dimethylacetal was also observed by NMR spectroscopy.[134]

Technical grade plant oils can also be employed directly as the crude triglyceride material. Under the conditions of isomerizing carbonylation, transesterification with methanol as a reagent and solvent to the respective methyl esters occurs simultaneously.[130,131] Alternatively, the respective plant oil methyl esters can be used as the crude material. Impurities in technical grade methyl esters do not influence the catalytic conversion significantly. Isomerizing alkoxycarbonylation of either starting materials results in the formation of linear *α*,*ω*-diesters with high selectivity. Monounsaturated fatty acids (e.g., oleic acid or palmitoleic acid) are transformed into saturated *α*,*ω*-diesters, and double unsaturated fatty acids are transformed into monounsaturated *α*,*ω*-diesters that can be transformed into the respective saturated analogues by hydrogenation of the crude reaction mixture (vide supra). Saturated fatty acids are unreactive in isomerizing methoxycarbonylation, but do not hinder the aforementioned transformations.

**Scheme 19. Isomerizing Methoxycarbonylation of Methyl Linoleate (top) with GC−FID Trace of Crude Reaction Mixture Showing Product Distribution (bottom)[a]**



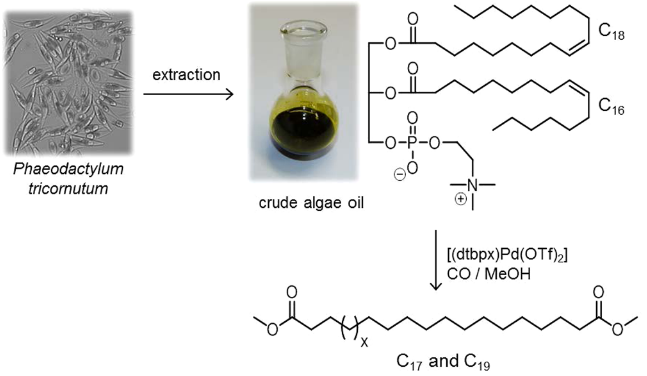
[a]Adapted from ref 132. Copyright 2013, The Royal Society of Chemistry.

We recently showed that even crude algae oil extracted from microalgae (*Phaeodactylum tricornutum*), which contains, in addition to saturated, monounsaturated (mostly palmitoleic, $C_{16}$; and oleic acid, $C_{18}$) and multiple unsaturated fatty acids (e.g., eicosapentaenoic acid, $C_{20}$), carotenoids, chlorophylls, carbohydrates, and phosphates as impurities, was readily transformed into the respective *α*,*ω*-diesters (Scheme 20).[135] This shows the exceptional versatility of this reaction and the remarkable robustness of the $[(\mathrm{dtbpx})\mathrm{Pd(OTf)_2}]$ catalyst precursor because impurities such as phosphate moieties could block coordination sites detrimentally, particularly for electrophilic cationic active species.

Concerning the scope of palladium-catalyzed isomerizing alkoxycarbonylation, it is notable that highly substituted double bonds of functionalized substrates can also be transformed selectively to the terminal product, as illustrated by terpenes.[136] Isomerizing methoxycarbonylation of the trisubstituted double bond of citronellic acid gave dimethyl-3,7-dimethylnonanedioate with full conversion and a selectivity of >95% for the terminal diester and an initial TOF of 3 $h^{-1}$ (0.4 mol % $[(\mathrm{dtbpx})\mathrm{Pd(OTf)_2}]$, 80 °C, 30 bar CO, 4 days, Scheme 21). Only minor amounts of a second diester were formed (<2% of dimethyl 3-(4-methylpentyl)pentanedioate). Hydromethoxylation to 7-methoxy-3,7-dimethyloctanoate occurred to a slightly larger extent as the only side reaction (10% by GC).

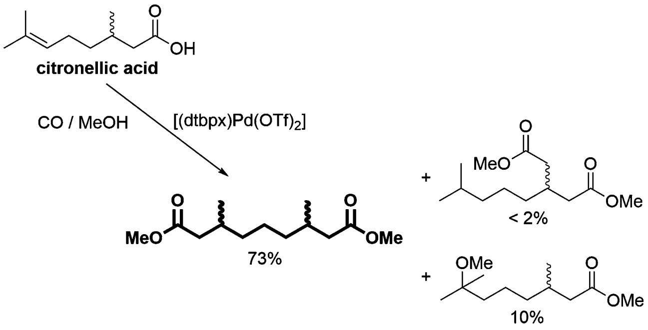
Most of the isomerizing functionalization approaches reviewed in the previous chapters generate unsymmetric

Scheme 20. Generation of Linear Long-Chain α,ω-Diesters from Crude Algae Oil with Isomerizing Methoxycarbonylation[a]



[a]Adapted from ref 135. Copyright 2014, John Wiley and Sons.

Scheme 21. Isomerizing Methoxycarbonylation of Citronellic Acid[136]



compounds with two different functional groups. In contrast, isomerizing alkoxycarbonylation of fatty acid esters yields symmetric α,ω-diesters. Several new pathways to valuable unsymmetric α,ω-difunctionalized, long-chain compounds were presented recently.[137,138]

A production of unsymmetric α,ω-diesters in isomerizing alkoxycarbonylation of methyl oleate with different alcohols is not possible under the aforementioned conditions because of extensive acid-catalyzed transesterification. One equivalent of acid is formed presumably during generation of the catalytically active Pd−hydride species from [(dtbpx)Pd(OTf)$_2$]. This can be neutralized by adding pyridine as a base, which enables the generation of unsymmetric α,ω-diesters with various alcohols (e.g., ethanol or benzyl alcohol) from methyl oleate (Figure 6, reaction a).[137] Cole-Hamilton and co-workers recently reported the aminocarbonylation of methyl 10-undecenoate and aniline with quantitative conversion to the desired linear amidoester (1.6 mol % Pd$_2$(dba)$_3$, ratio Pd/diphosphine/acid = 1/10/15, 2 equiv of aniline, 1.5 equiv of 2-napthol, 0.2 equiv of KI, 30 bar CO, 110 °C, 16 h; Figure 6, reaction b).[138] However, selectivities toward α,ω-amido esters from internal unsaturated esters were low. Another approach to long-chain unsymmetric α,ω-compounds was established by our group with isomerizing methoxycarbonylation of various N-functionalized substrates derived from oleic acid (Figure 6, reaction c−e).[137] Isomerizing alkoxycarbonylation of oleamide, oleonitrile, and *N*-oleylphthalimide gave the respective ω-ester-functionalized compounds with high conversions (70−96%). Transesterification did not occur to a significant extent under appropriate conditions. Note that oleonitrile and oleylphthalimide were stable even in the presence of methanol without any addition of base.

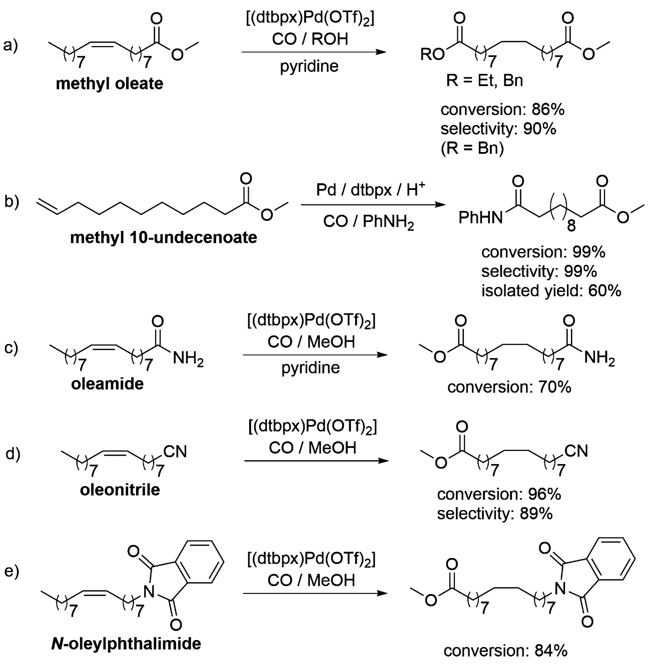


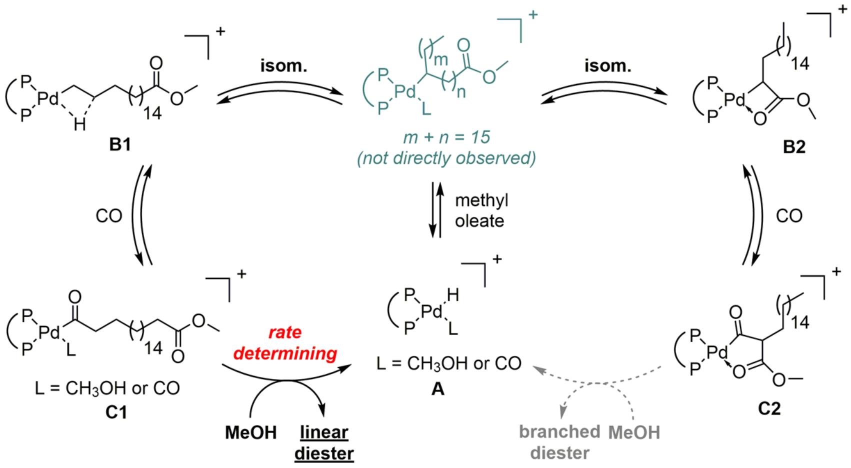
**Figure 6.** Isomerizing alkoxycarbonylation (a, c−e)[137] and aminocarbonylation (b)[138] for generation of unsymmetric α,ω-functionalized compounds; given conversions were determined by GC.

From our experimental and theoretical studies on isomerizing alkoxycarbonylation of fatty acids,[38,129,134] we were able to evolve a comprehensive mechanistic picture of this remarkable transformation. Low-temperature NMR spectroscopy allowed for the observation of relevant intermediates and the key features of the catalytic conversion of methyl oleate to the linear α,ω-diester with [(dtbpx)Pd(OTf)$_2$] (Scheme 22).[38]

Addition of stoichiometric amounts of methyl oleate to the catalytically active Pd−hydride species (**A**) results in formation of two distinct species: a linear Pd−alkyl species (**B1**) and a branched Pd−alkyl species (**B2**) that is stabilized by chelation of the ester group to the metal center. Both Pd−alkyl species rapidly insert CO and form defined Pd−acyl species (**C1** and **C2**). The linear Pd−acyl **C1** then undergoes methanolysis to form the linear diester and regenerates the catalytically active Pd−hydride species **A**. The methanolysis is the rate-determining step of the catalytic cycle. Contrary to its linear analogue, the chelated Pd−acyl **C2** resists methanolysis, and no significant amounts of the branched (here, malonic) ester are formed. This observation agrees qualitatively with results of pressure reactor experiments at elevated temperatures (90 °C) in which only small amounts of alkyl-branched side-products were formed (cf. Scheme 16). Whereas the first steps of functionalization, isomerization and CO insertion, are completely reversible, the rate-determining methanolysis is irreversible. Consequently, a formation of **C2** does not represent a dead end, but **C2** can interconvert with the productive catalytic cycle, leading to generation of the linear α,ω-diester product.

Further experimental and theoretical studies on the role of the ligand environment revealed that the steric demand around the Pd-center induced by the diphosphine ligand is responsible

**Scheme 22. Decisive Pathways of Isomerizing Methoxycarbonylation of Methyl Oleate with $[(dtbpx)Pd(OTf)_2]$ from NMR Studies at Low Temperature**[a]

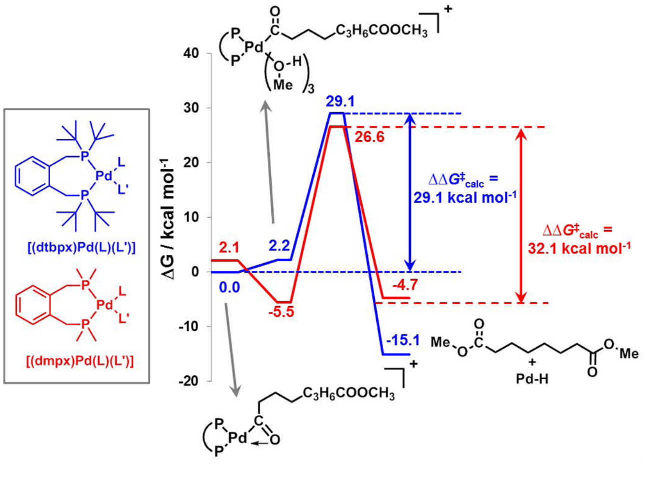


[a]Adapted from ref 38. Copyright 2012, American Chemical Society.

for both catalytic selectivity and catalytic productivity in isomerizing alkoxycarbonylation of plant oils. As outlined before, methanolysis is the rate-determining step of isomerizing methoxycarbonylation. DFT calculations suggested that the linear Pd−acyl species favors a cluster of three methanol molecules coordinated in the transition state of methanolysis rather than a single molecule transition state, which is favored for the methanolysis of branched Pd−acyl species.

Comparing the energetic barrier of methanolysis of the linear Pd−acyl species with the sterically demanding dtbpx as coordinating diphosphine ligand to the corresponding energy profile of dmpx ($1,2\text{-}(CH_2PMe_2)_2C_6H_4$) as a less bulky diphosphine ligand (Scheme 23), it becomes obvious that the higher energetic barrier for dmpx makes sterically less demanding ligands (such as dmpx) less productive ($\Delta G^{\ddagger}_{\mathrm{dtpbx}}$ = 29.1 kcal mol$^{-1}$ (blue) vs $\Delta G^{\ddagger}_{\mathrm{dmpx}}$ = 32.1 kcal mol$^{-1}$ (red)).

**Scheme 23. Energy Profile ($\Delta G$ in kcal mol$^{-1}$) of Ester Formation Starting from Linear Pd−Acyl Species $[(P\text{^}P)Pd(COC_6H_{12}COOCH_3)]^+$ for dtbpx (blue) and dmpx (red) Diphosphine Coordinated Pd-Species with Methyl Heptenoate As a Model Substrate**[a]



[a]$[(dtbpx)Pd(COC_6H_{12}COOCH_3)]^+$ as reference, set to zero.

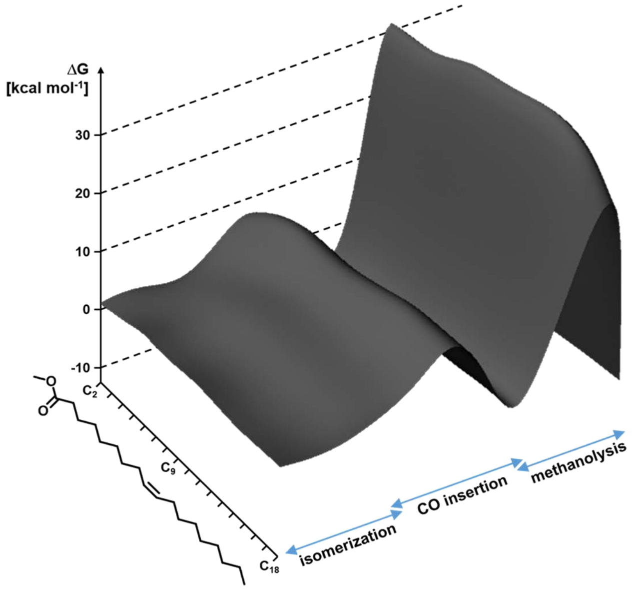
In addition, the differentiation of pathways yielding the linear diester and the alkyl-branched products is less pronounced. The calculated energetic barrier for methanolysis of the linear Pd−acyl species with dtbpx is 29.1 kcal mol$^{-1}$, and the methanolysis of the methyl-branched Pd−acyl (which leads to the main byproduct, the methyl-branched diester) is significantly higher ($\Delta\Delta G^{\ddagger}_{\mathrm{calc}}$ = 6.1 kcal mol$^{-1}$). The difference between methanolysis to the linear diester and methyl-branched diester for a dmpx-coordinated Pd-center is significantly smaller ($\Delta G^{\ddagger}_{\mathrm{calc}}$ = 32.1 kcal mol$^{-1}$ for methanolysis of linear $[(dmpx)Pd(COC_6H_{12}COOCH_3)]^+$, $\Delta\Delta G^{\ddagger}_{\mathrm{calc}} = \Delta G^{\ddagger}_{\mathrm{Me\text{-}branched}} - \Delta G^{\ddagger}_{\mathrm{lin}}$ = 1.5 kcal mol$^{-1}$). Therefore, sterically congested metal centers result in more selective and more productive catalysts.[134]

Scheme 24 summarizes this first unravelling of a selective catalytic isomerizing functionalization reaction sequence in a schematic energy landscape: The rate-determining step (in this case methanolysis) is preceded by a relatively flat energy landscape of the various reversible reaction pathways (Curtin-Hammett kinetics). This applies to the isomerization sequences (energy barriers around 6−12 kcal mol$^{-1}$), but also to the first reaction steps of functionalization (CO coordination and insertion, respectively, energy barriers between 8 and 18 kcal mol$^{-1}$). Effectively, these isomerization and functionalization steps are in mutual equilibrium. Selectivity arises from the differentiation of pathways in the final step of functionalization that has the highest energetic barrier.[134]

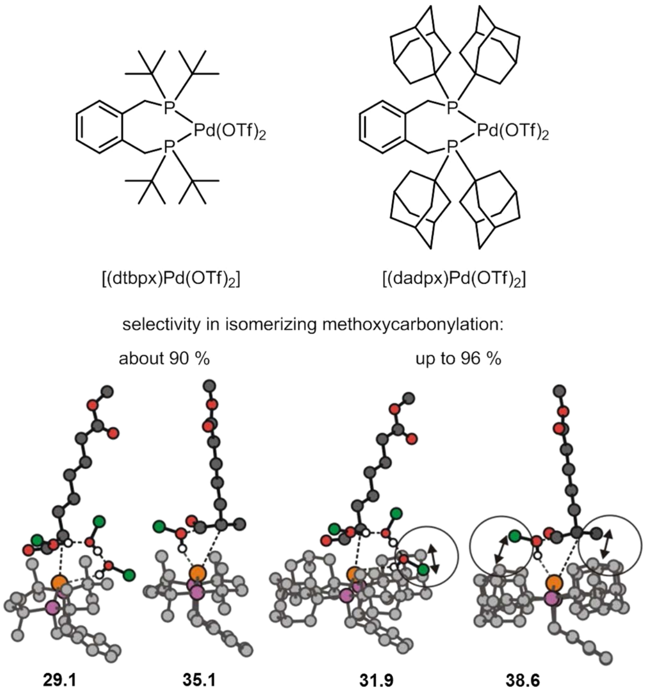
Further enhancement of the catalytic selectivity (up to 96%) was obtained by introducing adamantyl substituents (Scheme 25) to the diphosphine ligand.[139] By comparison with the established *tert*-butyl-substituted complex, steric congestion at the metal center is not increased. Rather, the rigid nature of the adamantyl substituents results in a specific interaction with the methanol substrate relatively remote to the metal center, which destabilizes the transition states of unselective pathways and thus results in higher energy differences of the desired reaction pathway leading to the linear product versus the various reaction pathways leading to branched products.

In summary, isomerizing alkoxycarbonylation is compatible with a broad spectrum of substrates, ranging from internal alkenes, monounsaturated fatty acid derivatives such as oleates, polyunsaturated fatty acid derivatives such as linoleates, and

**Scheme 24. Schematic Representation of the Energy Landscape of the Isomerizing Methoxycarbonylation of Methyl Oleate with Sterically Congested Pd(II) Centers, for Example $[(\text{dtbpx})\text{Pd}(\text{L})_2]^{n+}$**



**Scheme 25. Pd(II) Ditriflate Complexes of the Diphosphines dtbpx and dadpx (top) and Methanolysis Transition States of Linear (three-fold MeOH coordinated) vs Methyl-Branched Pd−Acyl Species (single MeOH coordinated) for dtbpx (bottom left) and dadpx (bottom right)[a,b]**



[a]The C-atom of MeOH is marked green for better visualization; ΔG in kcal $\text{mol}^{-1}$. [b]Adapted from ref 139. Copyright 2014, John Wiley and Sons.

plant oil triglycerides to crude algae oil diacylglycerides. The reaction is kinetically controlled and selectively gives the linear functionalized product in high yields.

## ■ COMPARATIVE CONSIDERATION OF OLEFIN METATHESIS AND ISOMERIZING FUNCTIONALIZATION REACTIONS

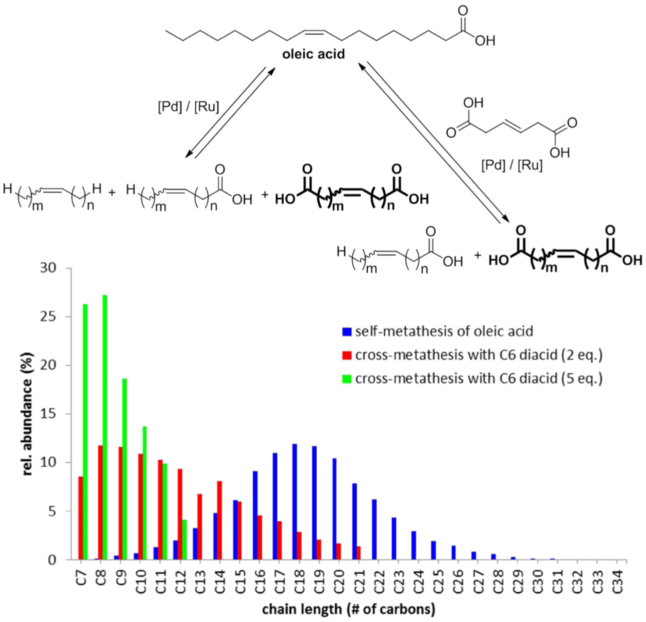
Metathesis reactions are versatile and convenient methods for transforming olefins, and they have been applied to almost any field of chemical synthesis. A comparison with the aforementioned isomerizing functionalization reactions is instructive here. Contrary to the latter reactions that are largely kinetically controlled, metathesis is an equilibrium reaction and often without any distinguished selectivity for a particular product. As outlined, the formation of α,ω-functionalized compounds from fatty acids via self-metathesis goes along with stoichiometric amounts of less valuable coupling products and is subject to a limited conversion unless selective removal of the product is possible.

**Olefin Metathesis and Isomerization.** Metathesis of fatty acids is well-established, and several approaches of combining an isomerization and a self-metathesis step have been reported.[19,140−145] Porri and co-workers observed the generation of a mixture of linear butenes, pentenes, hexenes, and olefins higher than $C_7$ from 1-pentene by isomerization and self-metathesis using an $[\text{IrCl}(\text{COE})_2]_2$-based catalyst that was activated with AgOTf (2 equiv) in the presence of trifluoromethanesulfonic acid (14 equiv).[142] Grubbs and co-workers used a similar system of 4 mol % $[\text{IrCl}(\text{COE})_2]_2$ activated with AgOTf (4 equiv) in isomerizing self-metathesis of methyl oleate. After hydrogenation of the reaction mixture, a mixture of linear $C_9$−$C_{26}$ alkanes, linear $C_8$−$C_{28}$ monoesters, and linear $C_{11}$−$C_{26}$ α,ω-diesters was obtained.[143]

Jackson and co-workers presented a one-pot metathesis−isomerization−methoxycarbonylation approach, which was applied to several fatty acid derivates, including methyl oleate, high oleic sunflower oil, and linseed oil.[144] The fatty acid esters were subjected to cross-metathesis with 2-butene and a second generation Hoveyda−Grubbs catalyst. The metathesis reaction was terminated by addition of ethyl vinyl ether when the equilibrium value was reached, and 2-butene was evaporated before alkoxycarbonylation (expect for linseed oil, which was alkoxycarbonylated without removal of 2-butene). The one-pot transformation was continued by addition of $\text{Pd}(\text{dba})_2$, dtbpx, methanesulfonic acid (ratio = 1/2.5/5), 28 bar CO, and methanol. Under these conditions, isomerizing alkoxycarbonylation gave rise to a mixture of esters ($C_6$, $C_9$, and $C_{12}$) and diesters ($C_9$, $C_{12}$) in a high linear selectivity (>95%). Only minor amounts of alkoxycarbonylated, but not metathesized, fatty acid and self-metathesized fatty acid were observed (<4%, <2%, respectively, for methyl oleate).

More recently, Gooßen and co-workers combined a dimeric palladium(I) isomerization catalyst $[\text{Pd}(\mu\text{-Br})\text{P}^t\text{Bu}_3]_2$ (0.6 mol %) and a NHC−indenylidene ruthenium metathesis catalyst (0.5 mol %) to convert oleic acid via self-metathesis into an equilibrium mixture of $C_8$−$C_{32}$ olefins, $C_{13}$−$C_{25}$ monocarboxylates, and $C_{13}$−$C_{22}$ α,ω-dicarboxylates (Scheme 26, NHC = N-heterocyclic carbene).[28] The same group reported isomerization/cross-metathesis between oleic acid and *trans*-3-hexenedioic acid (2 equiv) with a similar catalyst system (2.5 mol % Pd, 5.0 mol % Ru) under full conversion to a mixture of olefins, monocarboxylates, and α,ω-dicarboxylates close to equilibrium. By using a high-boiling solvent, the olefin fraction was continuously removed by distillation during the isomerization/metathesis, which resulted in a shift of the equilibrium toward the dicarboxylic acid fraction. It is important to note that (a) the ratio of oleic acid/*trans*-3-hexenedioic acid influenced the relative chain-length distribution and was shifted significantly to lower mean values compared with self-metathesis; (b) successful isomerization/cross-metathesis was not observed with acrylic acid or maleic acid as coupling partners because of inhibition of the isomerization catalyst by the acrylate moiety and the low reactivity of maleic acid.

**Scheme 26. Isomerization/Self-Metathesis of Oleic Acid (top, left pathway) and Isomerization/Cross-Metathesis of Oleic Acid with Hexenedioic Acid (top, right pathway) with Respective Chain-Length Distribution from Metathesis Reactions of Oleic Acid (bottom, as reflected by the olefin fraction, which is analytically easiest to access)**[a]



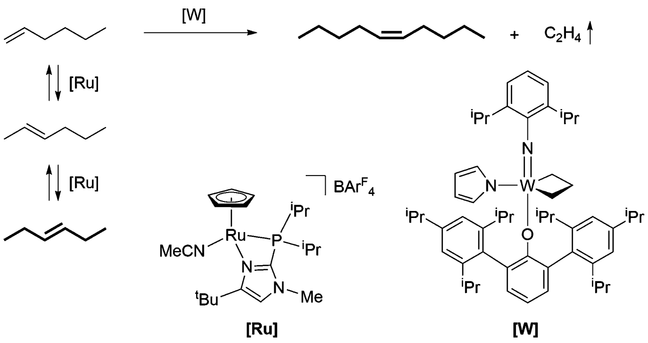
[a] Adapted from ref 28. Copyright 2012, American Chemical Society.

Nevertheless, none of these approaches results in the formation of a single compound in high selectivity, but rather, in mixtures of compounds with different chain lengths. Moreover, when methyl oleate or triglycerides of fatty acids with different numbers of double bonds are used as the substrate, mixtures of olefins, monocarboxylates, and *α*,*ω*-dicarboxylates can be formed.

Before this background, Schrock and co-workers recently presented a remarkable isomerizing metathesis approach that yielded a single product in high selectivity.[145] By combination of a ruthenium-based "alkene zipper" catalyst, that selectively isomerizes *trans*-internal olefins into a thermodynamic mixture of *trans*-olefins, and a tungsten-based *Z*-selective metathesis catalyst that reacts selectively with terminal olefins, transformation of *trans*-3-hexene into *cis*-5-decene and ethylene was possible with a selectivity of up to 64% (Scheme 27). In a typical experiment, 0.16 mol % of the tungsten metathesis catalyst and 0.05 mol % of the ruthenium isomerization catalyst were used in refluxing methylene chloride (40 °C) at a reaction time of 6 h. Conversion was 12.8% and, thus, relatively low; however, the selectivity of 64% is remarkable (this corresponds to an average TOF to the desired product of 11 $h^{-1}$).

A general problem in isomerization/metathesis reactions is further reaction cycles of the products initially formed (secondary metathesis). In the example of Schrock and co-workers, this translates into further isomerization/metathesis of *cis*-5-decene. This issue was overcome by application of a *Z*-selective metathesis catalyst that produces internal *cis*-olefins and an isomerization catalyst that exclusively isomerizes *trans*-olefins. Thus, a second isomerization/metathesis cycle is suppressed because the initial product *cis*-5-decene is unreactive toward both catalysts.

**Scheme 27. Isomerizing Metathesis of *trans*-3-Hexene to *cis*-5-Decene**[145]

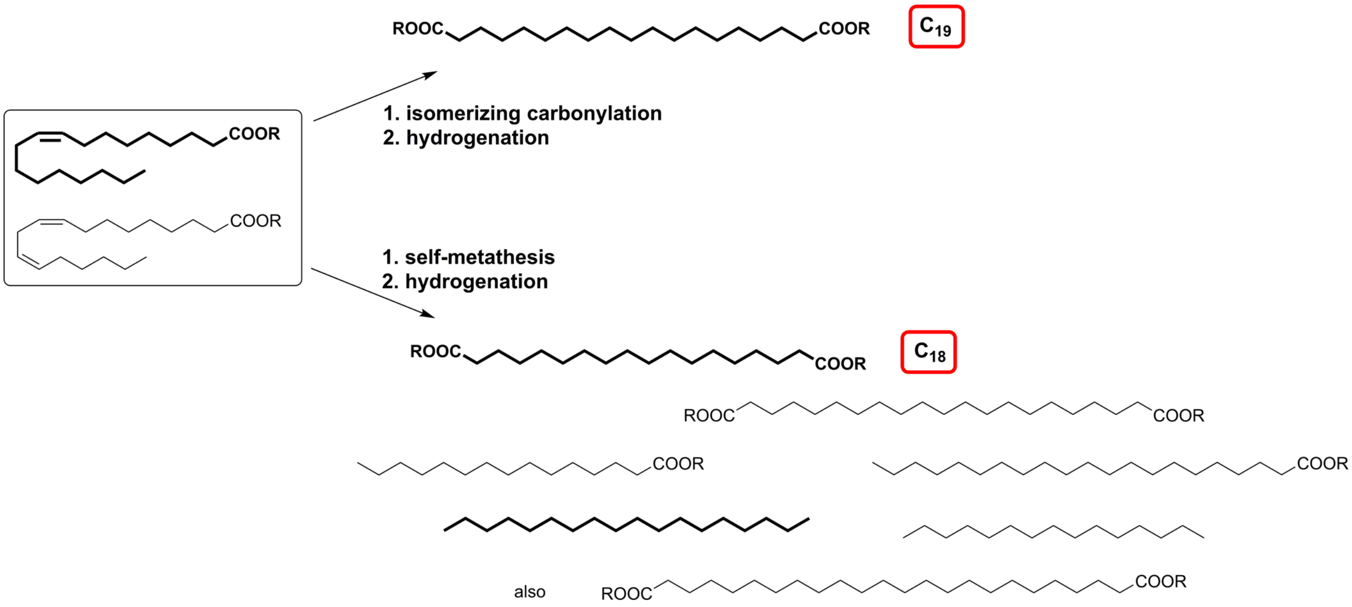


Regarding an envisioned analogous isomerization/metathesis of unsaturated fatty acids, secondary metathesis of the desired unsaturated *α*,*ω*-dicarboxylate products is less problematic because formation of terminal olefins by double bond isomerization is not possible from these compounds. However, a metathesis catalyst is required that (a) tolerates the carboxyl groups of the substrate and (b) is even more selective for terminal olefins than the tungsten-based catalyst used by Schrock and co-workers because the concentration of terminal olefins in a thermodynamic equilibrium is much lower for a longer-chain substrate (<0.2% for methyl oleate) versus the *trans*-hexenes (~1% of 1-hexene) used in their study.

**Isomerizing Functionalization Reactions vs Olefin Metathesis.** At this point, a direct comparison of olefin metathesis reactions (without an intentional additional isomerization step) and isomerizing functionalizations is instructive. The differences between isomerizing functionalization reactions, such as isomerizing carbonylations, and olefin metathesis can be related to fundamental characteristics of these transformations. Metathesis of a monounsaturated fatty acid (e.g., methyl oleate) and subsequent hydrogenation results in the formation of two types of products: the desired *α*,*ω*-diester and stoichiometric amounts of a nonfunctionalized alkane. Olefin metathesis as the first step of this conversion is an equilibrium reaction and thermodynamically controlled. Under ideal conditions, high turnover numbers can be reached, as Mol and co-workers showed with remarkably high effective turnover numbers >440 000 for the self-metathesis of methyl oleate with a second-generation Grubbs catalyst.[19] In contrast, isomerizing alkoxycarbonylation, as a concrete example, is strictly kinetically controlled, and the *α*,*ω*-diester product does not represent the thermodynamically favored outcome (Scheme 28).

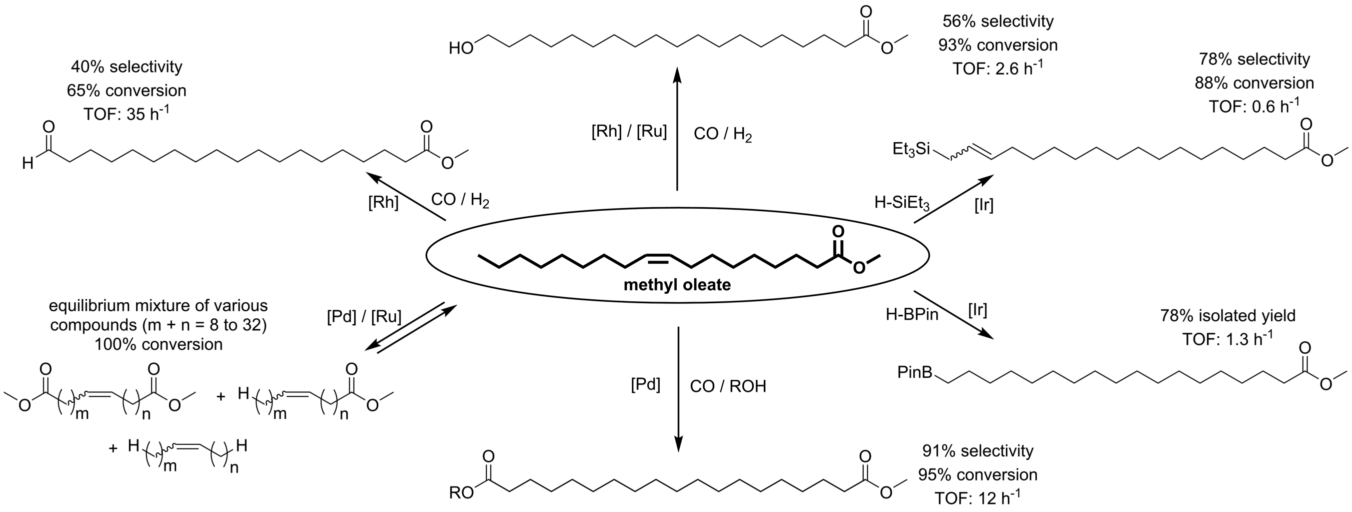
In terms of a complete utilization of the fatty acid feedstock for the generation of valuable *α*,*ω*-difunctional compounds, the kinetically controlled isomerizing alkoxycarbonylation is attractive compared with metathesis reactions because of the lack of formation of a stoichiometric coupling product. A clear advantage of metathesis reactions over many of the functionalization reactions is the exclusive formation of linear products. However, state-of-the-art isomerizing functionaliza-

Scheme 28. Comparison of Self-Metathesis Equilibria and Kinetically Controlled Isomerizing Carbonylation[a] of an Oleate Feedstock Also Containing Linoleate[b]



[a] Both with subsequent hydrogenation. [b] Bold structures show reaction products of monounsaturated oleate; regular structures show additional products (in addition to bold structures) from double unsaturated linoleate.

Scheme 29. Selected Catalytic Isomerizing *ω*-Functionalization Approaches of Fatty Acids, Exemplary Shown with Methyl Oleate



tions can compete in this regard, with a linear selectivity of up to 96%. Considering technical grade plant oil feedstocks, the inevitable presence of multiple unsaturated fatty acids must be taken into account. In metathesis, these will result in a range of additional products of different chain lengths (Scheme 28). In contrast, isomerizing alkoxycarbonylation can transform these compounds to the same product as obtained from their monounsaturated analogue (after hydrogenation of the remaining double bond). For other isomerizing functionalization reactions, the presence of multiple unsaturated fatty acid substrates in fatty acid feedstock is not sufficiently investigated yet and most published examples report the use of purified fatty acids.

## ■ SUMMARY AND CONCLUSIONS

The concept of isomerizing functionalization is particularly attractive for unsaturated fatty acids because *α*,*ω*-difunctional compounds with a long linear chain, representing the entire length of the substrates' natural methylene sequences, are accessible. These are attractive intermediates for chemicals and polymers. Approaches to meet the formidable challenge of converting the internal double bond to a functional group remote from its original position by, for example, eight carbon atoms, differ in their underlying principle, practicability, and scope. In addition, conversion rates and selectivities toward the desired product vary greatly for the different reactions (Scheme 29).

Isomerizing hydroboration differs from other transformations in that the desired terminal boron-functionalized fatty acid is clearly the thermodynamically most stable product in this case. The best results for methyl oleate were obtained by iridium-nanoparticle catalysis, with excellent isolated yields but low reaction rates.[101] Rhodium-catalyzed isomerizing hydroboration is very selective for nonfunctionalized olefins, but it has not been reported for fatty acids or other unsaturated esters so far. Compared with the reagents of other isomerizing functionalizations, the boron reagents are relatively costly and not practicable on a large scale. Furthermore, an additional step is required to generate functional groups of choice. On the other hand, a large scope of functional groups is accessible in this way.

Isomerizing silylation offers many pathways to various functionalized fatty acids, but isomerization of the starting material and selective terminal functionalization appear to be challenging and hinder the utilization of the full potential of this transformation. Until now, only one successful isomerizing dehydrogenative silylation with selective terminal silylation has been reported for methyl oleate.[111] Whereas selectivity and conversion were good, the reaction rate was poor. In general, the reactivity and utility of the products varies strongly with the silicon reagent employed. Tetraalkyl silanes as products are largely inert, whereas alkoxysilanes or chlorosilanes, for example, offer themselves for purposes such as surface modification or cross-linking.

Isomerizing carbonylations employ readily available reagents; namely, carbon monoxide and alcohols or hydrogen. Catalytic carbonylation in general is an established technology. Isomerizing hydroformylation is well worked out for nonfunctionalized internal alkenes, such as octenes,[39] but it is challenging to utilize on fatty acids. Formation of the linear $\alpha,\omega$-ester aldehyde is accompanied by large amounts of hydrogenated starting material; therefore, to date, only low selectivities have been reported.[64] For rhodium-catalyzed hydroformylation, it has been stated that large diphosphine bite angles increase the steric bulk around the metal center, which in turn induces a higher isomerization activity and an increased selectivity toward the linear product. The formation of the terminal product is therefore kinetically preferred. Isomerizing hydroformylation and reduction, as a one-pot procedure, appear promising, and higher conversion and selectivities have been reported, but usually, mixtures of aldehydes and alcohols were obtained with low reaction rates. In addition, hydrogenation as a side reaction occurred to a major extent.[75]

Regarding its selectivity, conversion, and turnover frequencies, isomerizing alkoxycarbonylation stands out. This can be related to a lack of undesired side reactions such as olefin hydrogenation or further reaction of the primary products. In addition, this catalytic reaction is tolerant toward technical grade feedstocks containing monounsaturated as well as polyunsaturated fatty acid substrates. The remarkable kinetic preference for the desired terminal product can be understood from mechanistic studies, which also reveal the general picture of an isomerizing functionalization reaction. Here, the barriers for isomerization and carbon monoxide insertion as a first step of functionalization are rather low, and the energy landscape is flat, such that all linear and branched intermediates are accessible and interconverting. The selectivity in the rate-determining step of functionalization, which is alcoholysis here, is enhanced by a sterically crowded environment at the metal center, which also lowers the energy barrier. Obvious challenges are an increase in the reaction rates, and selective and rapid reactions of multiple unsaturated substrates.

Related to these approaches, combinations of isomerization with olefin metathesis also appear attractive for fatty acid substrates, in principle. This is particularly interesting because highly active metathesis catalysts are already well-known and investigated;[19] however, the equilibrium outcome and lack of very specific reactivity for different olefin substrates of most metathesis reactions favor the formation of a statistical distribution of products with different chain lengths. A generic concept toward this issue remains to be developed.

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### Notes

The authors declare no competing financial interest.

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