Renewable Raw Materials

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Oils and Fats as Renewable Raw Materials in Chemistry

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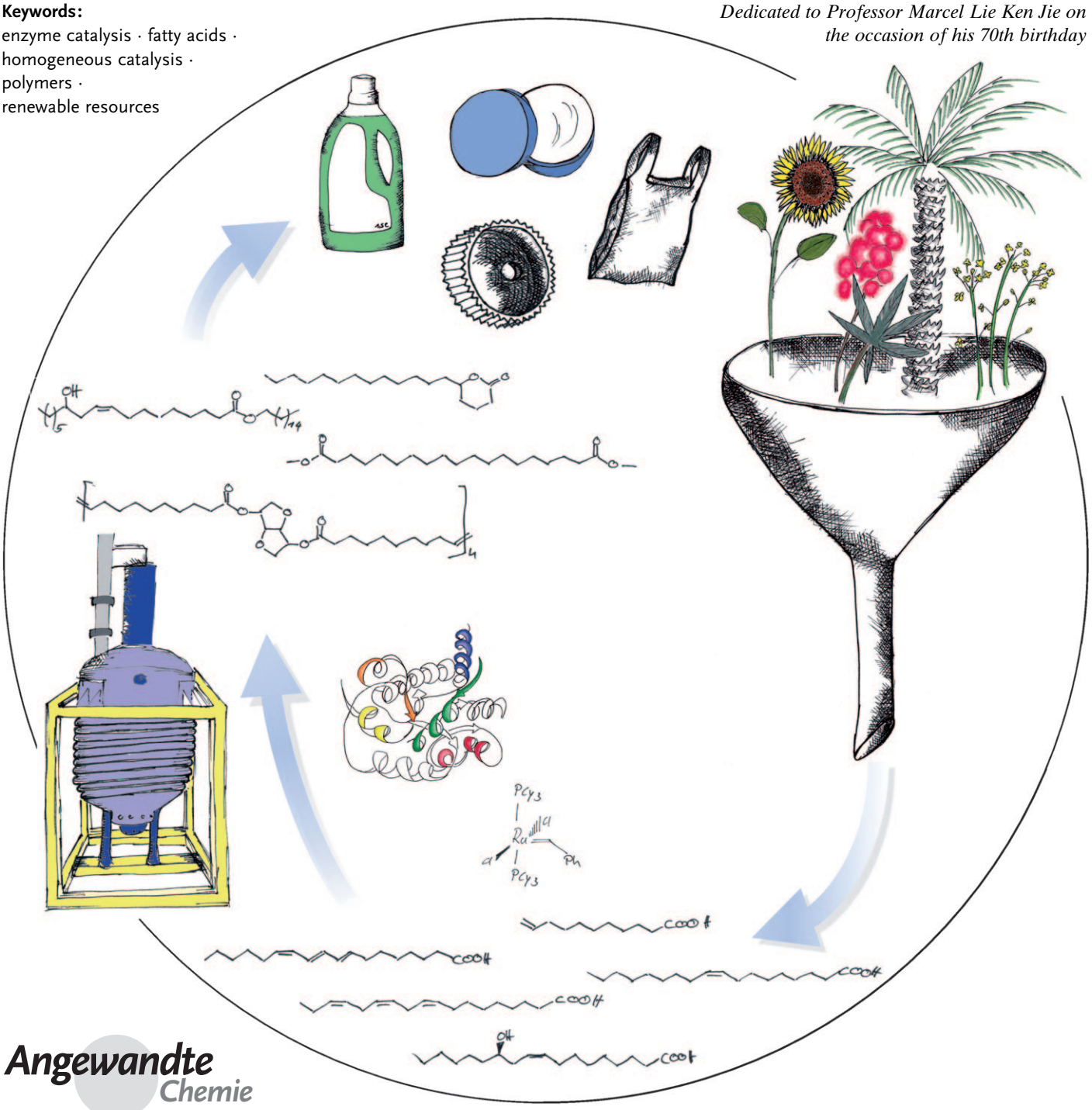
Dedicated to Professor Marcel Lie Ken Jie on the occasion of his 70th birthday



Oils and fats of vegetable and animal origin have been the most important renewable feedstock of the chemical industry in the past and in the present. A tremendous geographical and feedstock shift of oleochemical production has taken place from North America and Europe to southeast Asia and from tallow to palm oil. It will be important to introduce and to cultivate more and new oil plants containing fatty acids with interesting and desired properties for chemical utilization while simultaneously increasing the agricultural biodiversity. The problem of the industrial utilization of food plant oils has become more urgent with the development of the global biodiesel production. The remarkable advances made during the last decade in organic synthesis, catalysis, and biotechnology using plant oils and the basic oleochemicals derived from them will be reported, including, for example, ω-functionalization of fatty acids containing internal double bonds, application of the olefin metathesis reaction, and de novo synthesis of fatty acids from abundantly available renewable carbon sources.

From the Contents

1. Introduction

The UN World Summit on Sustainable Development, held in Johannesburg in 2002, called for the promotion of a sustainable use of biomass.[1] It was recently shown that biomass can be produced in a volume sufficient for industrial utilization without compromising the food supply for the increasing global population.[2] Chemists have much to contribute to meet this challenge.[3,4] Oils and fats of vegetable and animal origin are historically and currently the most important renewable feedstock of the chemical industry. Classical and well-established oleochemical transformations occur preferentially at the ester functionality of the native triglycerides,[5] such as hydrolysis to free fatty acids and glycerol[6] and transesterification to fatty acid methyl esters. Fatty acids are transformed by reactions at the carboxy group to soaps, esters, amides, or amines. Hydrogenation of both fatty acids and their methyl esters gives fatty alcohols, which are used for the production of surfactants.[7] Competitive petrochemical processes to produce fatty alcohols, such as the Ziegler Alfol process and hydroformylation of alkenes, exist, but the share of fatty alcohols from renewable resources is steadily increasing, from about 50% in 2000 to just under 65% in 2010.[7,8]

The basic oleochemicals (Scheme 1) are fatty acids (ca. 52%), the respective methyl esters (ca. 11%), amines (ca. 9%), and alcohols (ca. 25%).[9] These are used for the production of important product groups,[6] that is, surfactants,[10,11] lubricants,[12,13] and coatings.[14] The production volume of fatty acid methyl esters strongly increased during the last ten years because of their large-scale utilization as biodiesel,[15–17] giving as side product about 10 wt% of glycerol which has to be utilized. This fact stimulated research on glycerol as a platform chemical for the production of bulk chemicals, that is, 1,2- and 1,3-propanediol, acrylic acid, or epichlorohydrin.[18–20] The latter is an especially interesting development, since during the second half of the last century glycerol was petrochemically produced based on propene via epichlorohydrin.

Most of the native oils contain unsaturated fatty acids, such as oleic acid (**1a**), which is a *cis*-configured alkene and thus allows, in principle, the application of the well-known reactions of petrochemical alkenes. Remarkably, only very few reactions across the double bond of unsaturated fatty compounds are currently applied in the chemical industry (i.e., hydrogenation, ozone cleavage, and epoxidation). Moreover, there are no industrial processes utilizing selective C–H functionalization of the alkyl chain of saturated and unsaturated long-chain fatty acids. Interesting exceptions are the production of C2-branched Guerbet alcohols from fatty alcohols[7] and the microbial ω-oxidation of methyl oleate **1b** to *cis*-octadec-9-endioic acid dimethyl ester.[21] The latter is an example of the amazing opportunities offered by enzymatic and microbial reactions.

Fatty acids of plant seed oils show a remarkable variety.[22–24] In contrast, the fatty acids of bulk oils currently used in

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oleochemistry are rather uniform. Saturated fatty acids with an even number of carbon atoms (C8–C18) and unsaturated C18 fatty acids, such as **1a** and linoleic acid (**2a**) as well as relatively small amounts of linolenic acid (**3a**), erucic acid (**4a**), and ricinoleic acid (**5a**) are industrially utilized. The most important oleochemical reactions performed with **5a** are the thermal cleavage to 10-undecenoic acid **13a**[25] and basic cleavage to sebacic acid (decanedioc acid).[26] Interestingly, the enantiomeric purity of **5a**, which makes it an interesting substrate for organic synthesis, has not yet been exploited appropriately (for some examples, see Sections 3.2 and 3.3). The latter applies generally to the utilization of the synthetic potential of nature.

Thus, it will be important to introduce and to cultivate more and new oil plants that provide fatty acids with new and interesting properties for chemical utilization, such as petroselinic acid (**6a**) from the seed oil of *Coriandrum sativum*, (5Z)-eicosenoic acid (**7a**) from meadowfoam (*Limnanthes alba*) seed oil,[27] calendic acid (**8a**) from *Calendula officinalis*,[28] and α-eleostearic acid (**9a**) and punicic acid (**10a**) from tung (chinese wood) oil[22] and pomegranate,[29] respectively. Santalbic acid (**11a**) is the main fatty acid of the seed oil of the sandalwood tree,[30] and it, together with vernolic acid (**12a**) from *Vernonia galamensis*,[31] offers interesting synthetic applications. The cultivation of the respective plants for the production of these oils would increase the agricultural biodiversity, an important aspect of a sustainable utilization of renewable feedstocks. Moreover, classic breeding as well as genetic engineering will be necessary to improve the oil yield and the fatty acid composition for chemical utilization.[32–35]

In the 1980s, basic and applied research was intensified to tackle these challenges. The results obtained until the end of the century were reviewed in 2000.[36] It was stated: "With the breeding of new oil plants—including the use of gene technology—numerous fatty compounds of adequate purity are now available which makes them attractive for synthesis. The use of modern synthetic methods together with enzymatic and microbial methods has led to an extraordinary expansion in the potential for the synthesis of novel fatty compounds, which are selectively modified in the alkyl chain. … However, numerous synthetic problems remain unsolved and solutions must be found in the coming years."[36a]

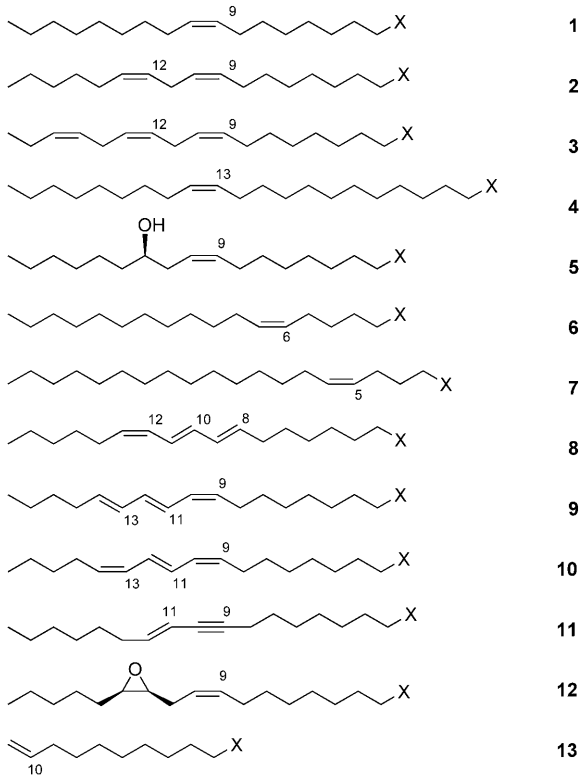
Ursula Biermann studied food chemistry in Hannover and Munich. She received her doctorate at the Technische Universität München in 1979 under W. Grosch. Since 1987 she has been a research fellow under J. O. Metzger at the Institute of Pure and Applied Chemistry of the Universität Oldenburg, where she works on the synthesis of novel fatty compounds using natural oils and fats as chemical raw materials. The main focus of her studies lies in Lewis acid induced, radical, and thermal addition reactions to the C–C double bond of unsaturated fatty compounds.

Uwe T. Bornscheuer (born 1964) studied chemistry and completed his doctorate in 1993 at the University of Hannover. He then was a postdoc at the University of Nagoya (Japan). In 1998, he completed his habilitation at the University of Stuttgart at the Institute of Technical Biochemistry. He has been professor at the Institute of Biochemistry at the University of Greifswald since 1999. Bornscheuer edited and wrote several books, is Editor-in-Chief of Eur. J. Lipid Sci. Technol., and is co-chairman of the Editorial Board of ChemCatChem. In 2008, he received the BioCat2008 Award for his innovative work on tailored biocatalysts for industrial applications. He was president of the Deutsche Gesellschaft für Fettwissenschaften e.V. from 2007 to 2009. His current research focuses on protein engineering of enzymes from various classes with special emphasis on the synthesis of chiral compounds and on lipid modification.

Michael A. R. Meier (born 1975) studied chemistry at the University of Regensburg and obtained his doctorate in 2006 from the Eindhoven University of Technology, for which he was awarded with the Golden Thesis Award of the Dutch Polymer Institute. In 2006 he was appointed principal investigator of the junior research group Renewable Raw Materials at the University of Applied Sciences in Emden, Germany. In June 2009 he was named junior professor for Sustainable Organic Synthesis at the University of Potsdam, Germany. He has been full professor at the Karlsruhe Institute for Technology in Karlsruhe, Germany, since October 2010. In 2010 he was awarded with the European Young Lipid Scientist Award of the European Federation for the Science and Technology of Lipids. His current research focuses on a sustainable use of plant oils and other renewable resources for the synthesis of novel monomers, fine chemicals, and polymers.

Jürgen O. Metzger studied chemistry at the universities of Tübingen, Erlangen, Berlin, and Hamburg. He received his Ph.D. at the Universität Hamburg in 1970 and completed his habilitation at the Universität Oldenburg in 1983. In 1991, he was appointed professor of organic chemistry, and he retired in 2006. His research areas include sustainability in chemistry, environmentally benign organic synthesis, renewable raw materials, radical chemistry, and mass spectrometry.

Hans Jürgen Schäfer (born 1937) studied chemistry at the University of Heidelberg and received his doctorate there on anionic rearrangements. From 1964 to 1966 he worked on the mechanism of the chromic acid oxidation at Yale University and completed his habilitation at the University of Göttingen in 1970 on the topic "Anodic dimerization and addition". In 1973 he was appointed full professor at the University of Münster, from where he retired in 2002. His main research interests are in the areas of organic electrosynthesis, conversion of renewable raw materials, and amphiphiles and their surface properties in the macro- and nanoscopic realms.



X	COOH	COOMe	CH_2OH
	a	b	c

Scheme 1. Fatty compounds as starting materials for synthesis: oleic acid (**1a**), linoleic acid (**2a**), linolenic acid (**3a**), erucic acid (**4a**), ricinoleic acid (**5a**), petroselinic acid (**6a**), 5-eicosenoic acid (**7a**), calendic acid (**8a**), α-eleostearic acid (**9a**), punicic acid (**10a**), santalbic acid (**11a**), vernolic acid (**12**), 10-undecenoic acid (**13a**), and the respective methyl esters (**1b–13b**) and alcohols (**1c–13c**).

Below, the advances made in the chemistry and biotechnology of fatty compounds over the last ten years will be discussed. Moreover, the importance of cultivating new oil plants for chemical usage of the oil will be addressed briefly. Glycerol is not included because its utilization was broadly reviewed quite recently.[18–20]

2. Commodity Plant Oils and Fatty Acid Production

The annual global production of the major vegetable oils (from palm, soy, rapeseed, cotton, peanut, sunflower, palm kernel, olive, and coconut) amounted to 84.6 million tons (Mt) in 1999/2000 and increased to 137.3 Mt in 2009/10 (an increase of 62%).[37] In addition, about 3.8 Mt of minor plant oils (from sesame, linseed, castor, corn) and about 22.1 Mt of animal fats (tallow, lard, butter, fish) were produced and consumed in 1999, growing moderately to 4.4 Mt and 24.5 Mt, respectively, in 2008.[38,39] These vegetable oils and most animal fats are primarily produced in these large amounts for food purposes. Only castor and linseed oil are almost exclusively used for industrial applications. Interestingly, the production of castor oil increased by 38% from 435000 t per year in 1999 to 603000 t per year in 2008, whereas the production of linseed oil decreased by 12% from 734000 t per year in 1999 to 643000 t per year in 2008.[39]

The annual global production of oils and fats that are also used as oleochemical feedstock is shown in Figure 1 for 1999/2000 and 2009/10. The increase of the production of palm and

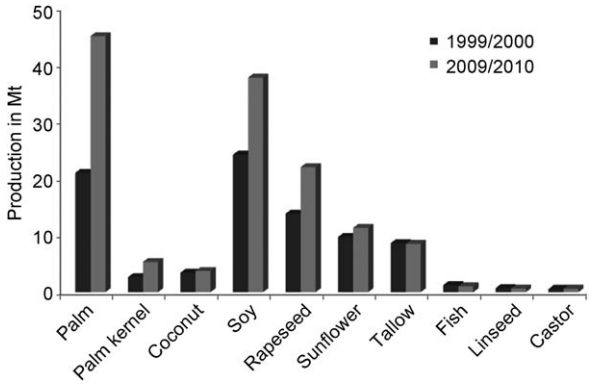


Figure 1. Production of oils and fats that are important as feedstock for the oleochemical industry in 1999/2000 and 2009/2010.[38,39]

palm kernel oil by more than 100%, followed by rapeseed oil (60%) and soybean oil (56%) is quite remarkable. The lauric oils from palm kernel (5.3 Mt in 2009) and coconut (3.7 Mt), the most important feedstock for the production of surfactants, give, in addition to the needed lauric (dodecanoic) and myristic (tetradecanoic) acid, about 10% and 6% capric (decanoic) and caprylic (octanoic) acid, respectively, making these fatty acids available as bulk chemicals. The globally averaged oil yield of soybean is 0.40 $t\,ha^{-1}$, of rapeseed 0.74 $t\,ha^{-1}$, and of sunflower 0.56 $t\,ha^{-1}$, whereas the oil palm produces more than 3.6 $t\,ha^{-}$ palm oil as well as 0.43 $t\,ha^{-1}$ of the industrially important palm kernel oil. The other three oil seeds supply additionally protein rich meals for feed.[40,41]

Traditionally, oil and fat consumption was shared between food, feed, and industrial use in the ratio 80:6:14. But with growing production of biodiesel this ratio is probably now closer to 74:6:20.[42] Palm and rapeseed oils contribute most to the growing industrial use, palm oil mainly because of the development of the oleochemical industry in southeast Asia and rapeseed oil mainly because of the biodiesel industry in Europe.[43] In 2008 biodiesel production and capacity amounted globally to 11.1 and 32.6 Mt, respectively.[44] The huge gap between capacity and production is most likely due to political reasons, such as the fluctuation of subsidies. This situation could offer an opportunity for the chemical industry, since biodiesel (a mixture of C16 and C18 fatty acid methyl esters) should be considered as a potential chemical feedstock. For instance, applications of biodiesel as a polymerization solvent have already been studied.[45,46]

The production of fatty acids is the highest volume oleochemical process and accounts for about 52% of

Table 1: Production and consumption of fatty acids[a] in 2000/2001 and 2008/2009 by regional distribution (in millions of tons).[47]

Region	2001 Production	2000 Consumption	2009[47b] Production	2008 Consumption
North America	1.13	1.19	1.00	1.32
western Europe	1.12	1.13	1.17	1.44
southeast Asia	1.20	n.a.[b]	4.76[c]	>2.62
rest of the world	0.35	n.a.[b]	0.74	0.49
global	3.80	n.a.[b]	7.76	>5.86

[a] Includes production of fatty acids from splitting of fats and oils and tall oil fatty acids. Excludes fatty acid salts by continuous soap making process. [b] Not available. [c] Malaysia (2.20 Mt), Indonesia (1.01 Mt), China (1.30 Mt).

industrially used oils and fats.[9] The world supply of fatty acids has almost doubled from 2001 to 2008.[47] Table 1 also reveals a tremendous geographical shift. Whereas production and consumption in North America and in western Europe was balanced in 2001, production remained almost constant in 2008, and consumption increased by 12 and 22%, respectively, using growing imports. In contrast, production and consumption exploded in southeast Asia, which has become the major producer and exporter of fatty acids and of fatty alcohols and methyl esters. At present, about 55–60% of global fatty acid production and capacity is located in southeast Asia owing to its proximity to the raw material sources. The region is the major source of palm, palm kernel, and coconut oil, and palm plantation companies are some of the major fatty acids producers.[47,48] In the oleochemical market, integration of palm plantation and oleochemical production is more pronounced, in contrast to the situation in North America and western Europe.

The geographical shift of fatty acid production has been accompanied by a relative feedstock shift from tallow to palm oil. Up to the 1990s, when the oleochemical industry was still concentrated in Europe and North America, about 60% of the oleochemically used oils and fats was tallow, followed by palm kernel and coconut oils (Figure 2). The doubling of fatty acid production up to 2008 is almost exclusively due to an increased use of palm oil (Table 1). In 2008, more than 66% of the global fatty acid production of over 6.7 Mt was derived from palm oil, palm kernel oil, and coconut oil. Consequently, the share of tallow declined to about 20%. Whereas only a small portion of the annually produced tallow can be consumed as edible fat, thus making the industrial utilization most appropriate,[22] palm oil is mainly used for food purposes. The problem of the industrial utilization of food plant oils has become more urgent with the development of the global biodiesel production.[43,44] Thus, Malaysian biodiesel export increased within a few years to 0.23 Mt in 2009.[49] Possibly, a scenario of cultivation of oil plants such as *Jatropha curcas* on degraded land, not competing with agricultural food production, would help to solve this problem and to supply sustainable biodiesel.[50]

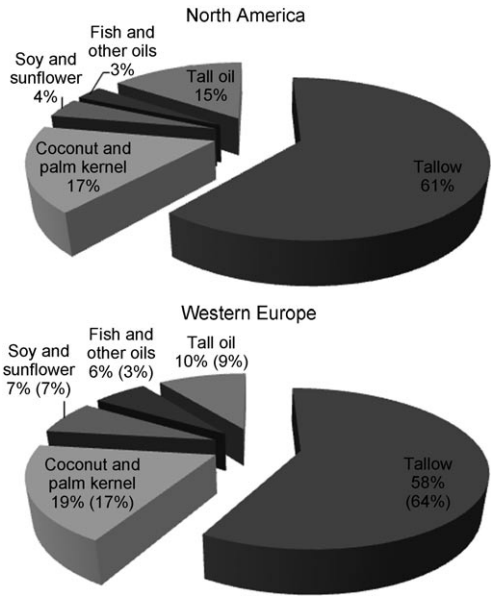


Figure 2. Feedstocks for the production of fatty acids in North America (USA, Canada) in 2008 (top) and in western Europe in 2008 (2000 in brackets, bottom). In southeast Asia almost exclusively palm oil including palm kernel and coconut oil is used.[47]

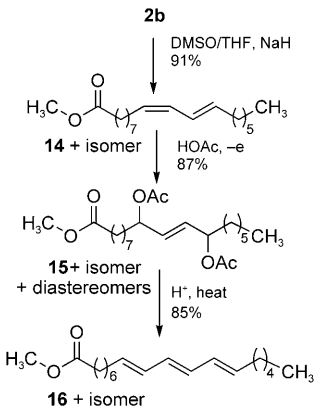
3. Reactions of Unsaturated Fatty Compounds

3.1. Oxidations

The oxidation of unsaturated fatty acids and vegetable oils has recently been reviewed with emphasis on epoxidation, bishydroxylation, and double-bond cleavage[51] and for lipids with focus on autoxidation, photooxidation, epoxidation, and oxidative cleavage.[52]

3.1.1. Double-Bond Oxidation

Double bonds can be oxidized by electron transfer and by chemical oxidants. The conjugated diene **14** (Scheme 2) was converted by anodic oxidation into the diacetate **15**, which



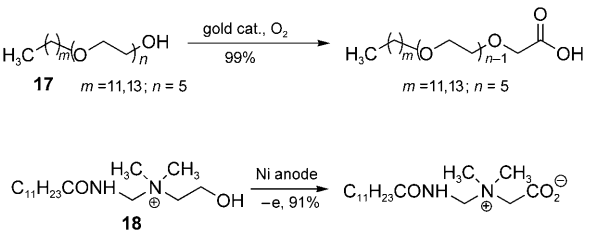
Scheme 2. Anodic oxidation of diene **14** to diacetate **15** and conversion of **15** to triene **16**.

was transformed into (*E*,*E*,*E*)-triene **16**.[53] Interestingly, **16** and its isomer are isomers of α-eleostearic acid **9a**, which occurs in Chinese tung oil and is used as component for water-resistant varnishes.

The ruthenium-catalyzed oxidative cleavage of unsaturated fatty acids was achieved in excellent yield (and avoiding CCl_4 as cosolvent) with 2.2% $RuCl_3$ and 4.1 equivalents $NaIO_4$ in water/MeCN (1:1) under sonication.[54] About 95% $NaIO_4$ can be saved by using the same reagents but reoxidizing the formed iodate back to periodate in an indirect electrochemical oxidation.[55] Osmium(VIII)-catalyzed double-bond cleavage of **1b** with dioxygen and aldehyde afforded 50–70% of the cleaved products. The oxidant in this case seems to be a peracid formed in situ.[56] Moreover, **1a** was cleaved to 30–35% azelaic acid (nonanedioic acid) with molecular oxygen in supercritical CO_2 over microporous molecular sieves (MCM-41) that contained chromium, cobalt, or manganese.[57]

3.1.2. Oxidation of Hydroxy Groups in Fatty Acid Derivatives

For economic and ecological reasons, molecular oxygen and the anode are attractive reagents for the oxidation of alcohols. The fatty alcohol ethoxylate **17** (Scheme 3) has been



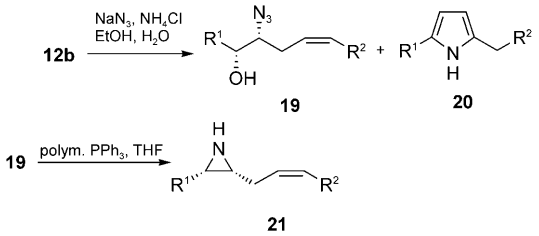
Scheme 3. Oxidation of ethoxylate **17** with molecular oxygen and of β-hydroxyethylammonium salt **18** at a nickel hydroxide electrode.

oxidized with dioxygen and a supported gold catalyst in high selectivity to the corresponding acid.[58] Similarly, the fatty acid monoethanolamide was converted to the corresponding *N*-acylglycinate.[59] At a nickel hydroxide electrode in 0.5 M NaOH, the β-hydroxyethylammonium salt **18** was oxidized to the glycine betain.[60]

3.1.3. Epoxidation and Products from Epoxides

Epoxides are prepared from hydroperoxides, hydrogen peroxide, or molecular oxygen with different catalysts.[51] High epoxide and diepoxide yields have been obtained from **1b**, **2b**, and **12b** with *tert*-butylhydroperoxide as oxidant and Ti-MCM-41 (an ordered mesoporous titanium-grafted silica) as catalyst. Advantages are acid-free conditions, easy removal of the catalyst by filtration, and a low oxidant excess.[61] With alumina (prepared by a sol–gel process) as catalyst, **1b** was epoxidized in high conversion with 70% aqueous hydrogen peroxide.[62] Moreover, the reaction of **1b** with molecular oxygen in the presence of aldehydes yielded up to 99% of the epoxide.[63]

Epoxides are versatile intermediates that can be converted by electrophilic or nucleophilic ring opening. For instance, epoxidized soybean oil was converted to carbonated soybean oil (CSBO) with CO_2 in 99% conversion using tin tetrachloride/tetrabutylammonium bromide as catalyst. Subsequently, CSBO was reacted with ethylene diamine to yield well-performing non-isocyanate-derived polyurethanes.[64] Methyl vernolate (**12b**) was used as starting material for the synthesis of a bolaamphiphile with potential application for targeted drug delivery to the brain.[65] Enantiomerically pure aziridines were obtained by a two-step synthesis starting from **12b**.[66] Treatment of **12b** with sodium azide in the presence of water afforded the azidoalcohol **19** and the pyrrole derivative **20** in approximately equal amounts (Scheme 4). Compound



Scheme 4. Synthesis of azidohydrin **19** and pyrrole **20** and conversion of **19** to enantiomerically pure aziridine **21**.[66] $R^1 = (CH_2)_4CH_3$, $R^2 = (CH_2)_7COOCH_3$.

19 was converted to aziridine **21** and **20** was reduced to the aminoalcohol. Bis- and tris-aziridines derived from **2a** and **3a**, respectively, showed cytotoxic, antimicrobial, and remarkable antitumor activities in combination with good neuroprotective effects.[66] Moreover, methyl *cis*-9,10-epoxyoctadecanoate was used for the synthesis of various fatty heterocycles, such as 4,5-dihydrooxazole, oxazolidine, imidazole, oxazole, and imidazolinethione.[67]

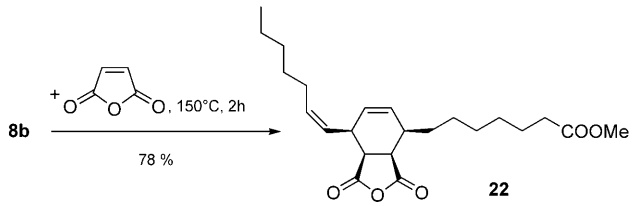
To synthesize oleochemicals with improved fluidity at low temperature, epoxides of different alkyl oleates have been converted with alkanoic acids into diesters in 72–83% yield.[68] Alkyl β-hydroxyethers were prepared from 9,10-epoxystearate and alkanols with saponite clay[69] or 10% sulfuric acid as catalyst.[70] Some of them exhibited favorable low-temperature flow characteristics.[70] Moreover, methyl 9,10-epoxystearate was converted without solvent and with only a minimal amount of catalyst with 2-hexanone and levulinic acid to cyclic ketals that are potential new hydrophobes for surfactants.[71] Good corrosion inhibitors were prepared from the epoxides of **1b** and **13b**,[72] and surfactants with tensidic properties equal to those from lauric oils have been obtained from **1a**, **4a**, and **7a** by epoxide ring opening.[73]

3.2. C—C-Bond-Forming Additions to the C—C Double Bond

3.2.1. Pericyclic, Ionic, and Radical Additions

Solvent-free Diels–Alder additions of maleic anhydride to the highly reactive hexatriene system of methyl calendulate (**8b**) and methyl α-eleostearate (**9b**), respectively, gave exclusively the all-*cis* cycloaddition products (e.g., **22**,

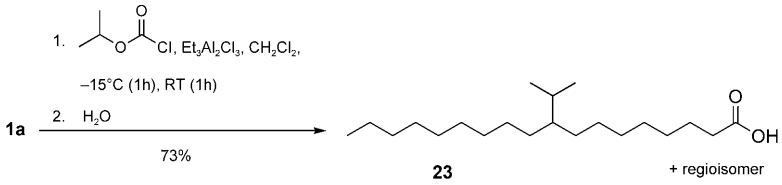
Scheme 5). A high regio- and stereoselectivity was observed for these additions to the conjugated *trans*-double bonds with retention of the *cis*-configured double bond.[74]



Scheme 5. Regio- and stereoselective Diels–Alder reaction of methyl calendulate (**8b**) and maleic anhydride.[74]

The esters of **8a** and **9a** were obtained by gentle transesterification of the respective native oils in the presence of sodium methoxide as catalyst. Especially ethyl and isopropyl calendula oil esters were described to show good properties as reactive diluents for alkyd resins in coating formulations.[75] Diels–Alder cycloadditions of conjugated linolenic acid (**14**) were performed using metal triflates, especially $Sc(OTf)_3$ and $Cu(OTf)_2$ as catalysts.[76]

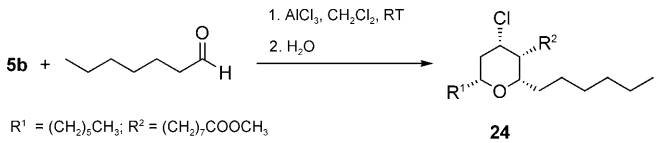
The synthesis of alkyl branched fatty compounds is of high importance owing to the interesting properties of the resulting materials in the cosmetic and lubricant area.[77] The Lewis acid induced hydroalkylation reaction using alkyl chloroformates has thus been developed as a new method for the alkylation of alkenes in general and of unsaturated fatty compounds in particular.[78] The reaction of, for example, oleic acid (**1a**) and isopropyl chloroformate in the presence of ethylaluminum sesquichloride ($Et_3Al_2Cl_3$) gave (roughly) a 1:1 mixture of the regioisomers 9- (**23**) and 10-isopropyloctadecanoic acid (Scheme 6). Concerning the mechanism of this



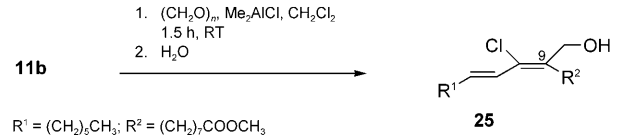
Scheme 6. $Et_3Al_2Cl_3$-induced hydroalkylation of oleic acid (**1a**) with isopropyl chloroformate.[78]

reaction, isopropyl chloroformate decomposes in the presence of $Et_3Al_2Cl_3$ by formation of CO_2 and of an isopropyl cation, which adds to the C–C double bond. Applying this new method, 1-propyl, 1-butyl, 1-pentyl, and 2-pentyl chloroformate could be used as alkylating agents.[78] Moreover, zeolite-catalyzed isomerizations of **1a** gave, after catalytic hydrogenation, branched-chain fatty acids with high conversions and high selectivity.[79] The mechanism of the isomerizations was postulated to proceed via three- and four-membered cyclic carbocation intermediates.[80]

Tetrahydropyrans are important building blocks in many biologically active natural products. $AlCl_3$-catalyzed cyclizations of **5b** with aldehydes, for example, heptanal,[81] proceeded with high diastereoselectivity and without epimerization to yield the enantiomerically pure all-*cis*-4-chlorotetrahydropyran **24** (Scheme 7). The corresponding montmorillonite KSF/O mediated reaction gave the all-*cis*-4-hydroxy compound. Moreover, highly regioselective cationic carbon–carbon bond-forming additions to the triple bond of the conjugated enyne system of santalbic acid **11a** were reported.[82] For instance, the dimethylaluminum chloride (Me_2AlCl)-induced addition of formaldehyde gave only one of the eight possible regio- and stereoisomers resulting in fatty acid ester **25** (Scheme 8).

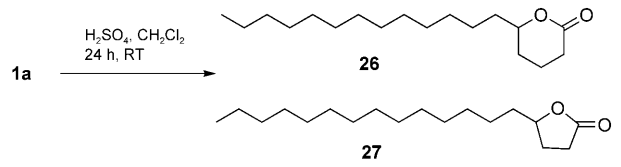


Scheme 7. $AlCl_3$-catalyzed cyclization of methyl ricinoleate **5b** with heptanal.[81]



Scheme 8. Me_2AlCl-induced regioselective and stereoselective reaction of methyl santalbate (**11b**) and paraformaldehyde to give fatty acid ester **25** in 76% yield.[82]

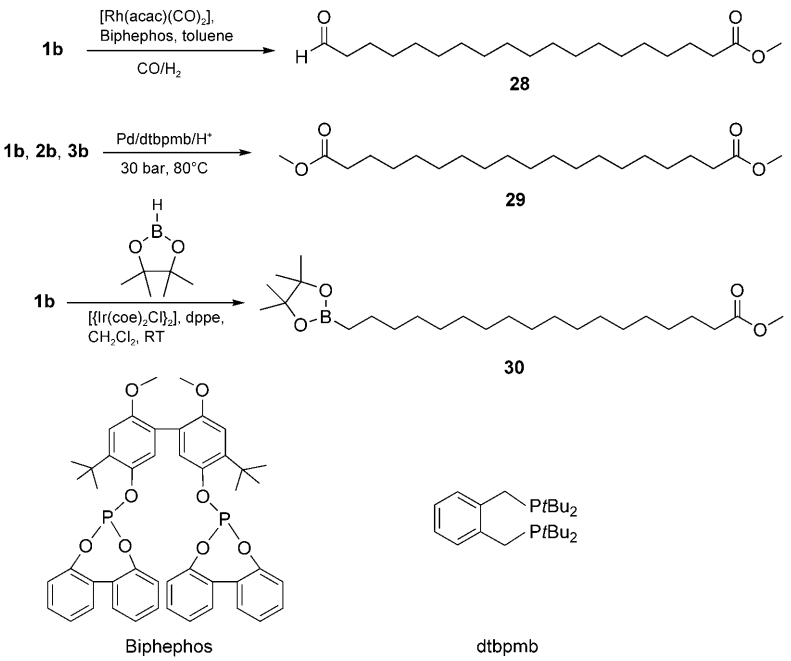
The treatment of unsaturated fatty acids, such as **1a**, with concentrated sulfuric acid in a polar, nonparticipating solvent, such as dichloromethane, allowed the synthesis of δ-stearolactone (**26**) together with the normally obtained thermodynamically more stable γ-stearolactone (**27**) as minor product (Scheme 9).[83] The well-known radical addition of thiols to unsaturated fatty compounds[84] has attracted renewed interest, and butanethiol has been added to canola and corn oils in UV-initiated reactions.[85] Sulfur-containing compounds are commonly introduced as additives to lubricant formulations to improve wear and friction properties by maintaining boundary-lubricating properties through physical and chemical adsorption to metal. Moreover, soy-based thiols and enes were formulated with allyl triazine, and UV curing resulting in tack-free coating films.[86]



Scheme 9. Synthesis of δ-stearolactone (**26**) from oleic acid (**1a**). γ-Stearolactone (**27**) was formed as side product ([**26**]:[**27**] = 15:1).[83]

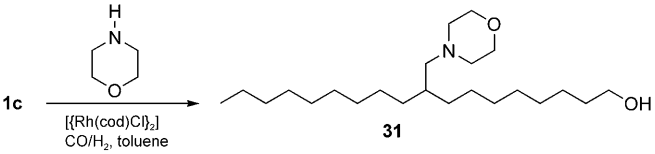
3.2.2. Transition-Metal-Catalyzed Additions

The development of the application of the many transition-metal-catalyzed reactions to the C–C double bonds of unsaturated fatty compounds has made important advances.[87,88] Very interestingly, the synthesis of ω-functionalized fatty acids using commonly available fatty compounds with internal C–C double bonds as substrate was described to proceed via an isomerization of the double bond along the fatty acid chain and an exclusive trapping of the ω-double bond. Thus, the isomerizing hydroformylation of **1b** and **2b** was performed in the presence of a rhodium catalyst to give the ω-aldehyde **28** in yields of only 26% and 34%, respectively (Scheme 10).[89] Unfortunately, hydrogenation of the double bonds was the dominating pathway. In contrast, α,ω-diacid esters were obtained by methoxycarbonylation catalyzed by Pd complexes with selectivities of greater than 95%.[90] Full conversion of **1b** as well as **2b** and **3b** gave dimethyl nonadecanedioate **29** (Scheme 10) under mild reaction conditions. Thus, most importantly, a mixture of unsaturated fatty acids **1a**, **2a**, and **3a**, commonly occurring in native plant oils, gives one single product. Interestingly, these compounds were already shown to be of high value for the synthesis of industrially relevant semi-crystalline polyesters from renewable resources.[90] Using a similar concept, the selective hydroboration of **1b** with pinacolborane at the terminal carbon atom was catalyzed by Ir to give product **30** (Scheme 10) in 45% yield.[91]

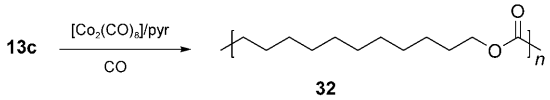


Scheme 10. Hydroformylation, methoxycarbonylation, and hydroboration of methyl oleate (**1b**) by isomerization of the internal and trapping of the terminal C–C double bond to give ω-functionalized fatty acid esters **28**,[89] **29**,[90] and **30**.[91] The synthesis of **29** is also possible using **2b** or **3b** as starting material. dppe: 1,2-bis(diphenylphosphino)ethane, coe: cyclooctene.

Hydroformylation of **1b** and some native oils using homogeneous rhodium catalysts was applied for the synthesis of novel bio-based polyols.[92–95] Homogeneous rhodium complexes were also used for the hydroaminomethylation of alkenes.[96] The reaction was applied to **1a** and **1c** using various primary and secondary amines and resulted in amino functionalized branched fatty acid derivatives, such as **31**. These compounds are useful intermediates for the preparation of surfactants and can be obtained in a simple one-pot reaction (Scheme 11).[97] Last but not least, a new method for the preparation of fat-derived linear polyesters that show good thermoplastic properties was developed using 10-undecenol (**13c**). Thus, **13c** and CO were copolymerized in the presence of tetracarbonylcobalt as catalyst to give poly(12-hydroxydodecanoate) (**32**, Scheme 12).[98]



Scheme 11. Hydroaminomethylation of **1c** with morpholine.[97] cod: cyclooctadiene.



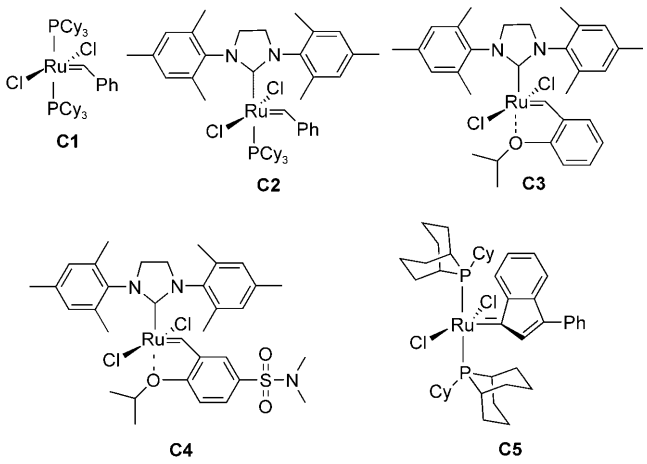
Scheme 12. Cobalt-catalyzed copolymerization of **13c** and CO to give polyester **32** ($M_n > 10^4$ g mol^{-1}).[98] pyr: pyridine.

3.3. Metathesis Reactions

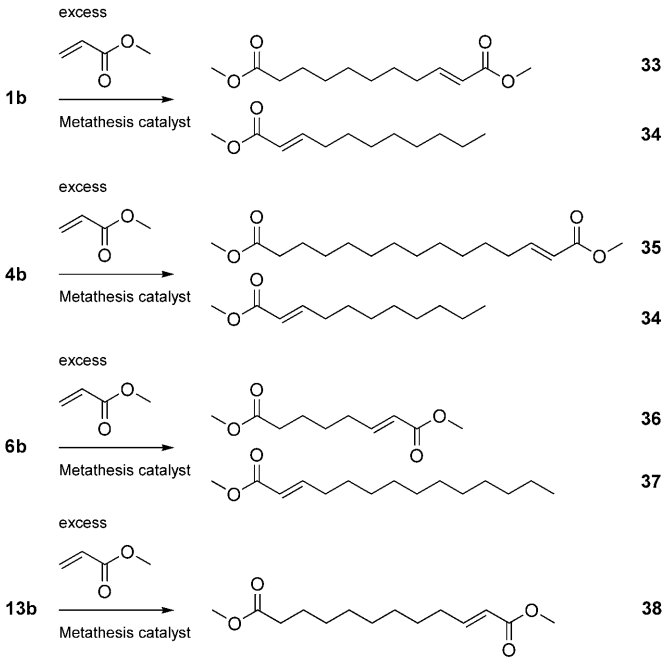
3.3.1. Monomers and Platform Chemicals

Since the pioneering work of Boelhouwer and co-workers in 1972,[99] olefin metathesis reactions with fatty acid derivatives have made considerable progress.[100,101] Particularly the last 10 years have brought about significant improvements, making olefin metathesis one of the most versatile tools in oleochemistry.[100] One of the main reasons for this advance was the development of functional-group-tolerant metathesis catalysts by Grubbs and others,[102] thus allowing the reduction of the catalyst amounts as well as transformations with olefins containing functional group (Scheme 13).

Especially the synthesis of ω-functionalized fatty acids by cross-metathesis (CM) was heavily researched over the last few years. One of the still most frequently investigated topics in this context is the ethenolysis of **1a** and its derivatives leading to 9-decenoic acid and 1-decene, two important platform chemicals for polymers and surfactants from renewable resources.[111]



Scheme 13. Ruthenium-based metathesis initiators used for the transformation of fatty acid derivatives: **C1**: first-generation Grubbs catalyst;[103,104] **C2**: second-generation Grubbs catalyst;[105,106] **C3**: second-generation Hoveyda–Grubbs catalyst;[107] **C4**: commercially available Zannan catalyst with an activating electron-withdrawing group (similar to systems developed by Grela et al.);[108,109] **C5**: Phoban indenylidene catalyst discussed by Winde and co-workers for metathesis reactions of **1b**.[110] Cy: cyclohexyl.



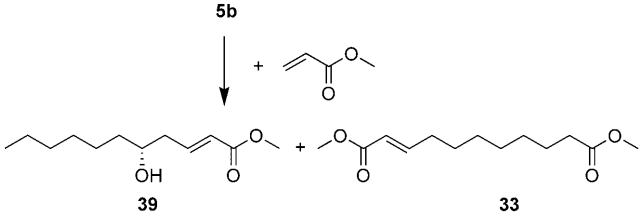
Scheme 14. Cross-metathesis of fatty acid methyl esters with methyl acrylate to yield diesters with different chain lengths.[118]

Warwel et al. showed that the ethenolysis of fatty acid derivatives is possible with very low amounts of **C1** (0.01 mol% or less) and that the resulting 9-decenoic acid methyl ester can be dimerized with **C1** to yield a long-chain α,ω-diester for polyester synthesis.[112,113] The resulting linear ω-unsaturated fatty acids are also of interest as monomers for copolymerization with alkenes such as ethene and propene using homogeneous metallocene/methylaluminoxane catalysts[114] as well as Brookhart catalysts.[115] Interesting properties and applications can be expected for these polymers.

Other recent developments discuss, for instance, that the ethenolysis proceeded well in ionic liquids with the potential of catalyst recycling[116] and that new ruthenium- (**C5**)[110] and molybdenum-based[117] metathesis initiators showed promising results for this reaction. The first systematic study concerning the synthesis of α,ω-diesters with different chain lengths by cross-metathesis of fatty acid esters with methyl acrylate was published in 2007 by Meier et al.[118] Catalyst **C3** provided full conversions and good selectivities at low catalyst loadings (below 0.5%), but only if the reactions were performed under solvent-free conditions. This finding is especially noteworthy, as CM reactions with the electron-deficient methyl acrylate usually require much higher catalyst loadings.[118] Thus, a variety of diesters with different chain lengths was obtained, taking full advantage of nature's synthetic potential (Scheme 14). These compounds (**33, 35, 36, 38**) have possible applications in polyester and polyamide synthesis and, owing to their different chain lengths, can cover a broad range of properties of these materials. Moreover, shorter chain monoesters obtained as a second product are suitable starting materials for detergent applications. Along the same lines, Dixneuf and co-workers described the cross-metathesis of fatty acid methyl esters with acrylonitrile to yield ω-cyano fatty acid esters.[119] Self- and cross-metathesis reactions of 10-undecenal (the aldehyde derived from **13**, with acrolein, acrylonitrile, acrylic acid, and methylacrylate) were also described to result in interesting additional α,ω-bifunctional fatty acid derivatives.[120]

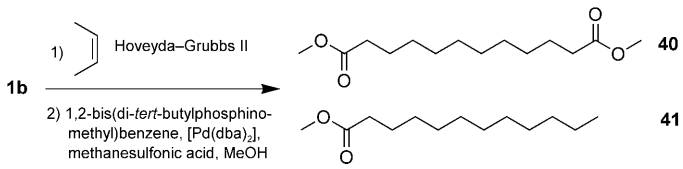
Furthermore, ω-chlorine-substituted derivates were prepared from **1b** and **13b** by CM with allylchloride.[121] In addition, the CM of fatty alcohols was investigated and showed undesired side reactions as well as low conversions and selectivities,[122] most likely because alcohols can degrade the ruthenium-based metathesis catalysts.[123] To circumvent this problem, the desired ω-hydroxy fatty acid esters were prepared by CM of acetate-protected fatty alcohols with methyl acrylate in an efficient catalytic reaction.[122] In contrast, a protecting-group strategy was not necessary when cross-metathesis reactions of **5b** (Scheme 15) were investigated, thus indicating that secondary alcohols are tolerated better by the investigated catalysts (**C3** and **C4**).[124]

High turnover numbers (above 9500) were also achieved for the CM of **1b** with 2-butene,[125] and the reaction could be coupled to a one-pot sequence of isomerization, methoxycarbonylation, and transesterification for the efficient synthesis of terminal oxygenates from renewable resources.[126]



Scheme 15. Cross-metathesis of **5b** with methyl acrylate to yield two monomers for polyesters (note: **39** is chiral).[124]

This elegant tandem reaction also leads to a valuable α,ω-bisfunctional polycondensation monomer **40** from plant oils, as depicted in Scheme 16.



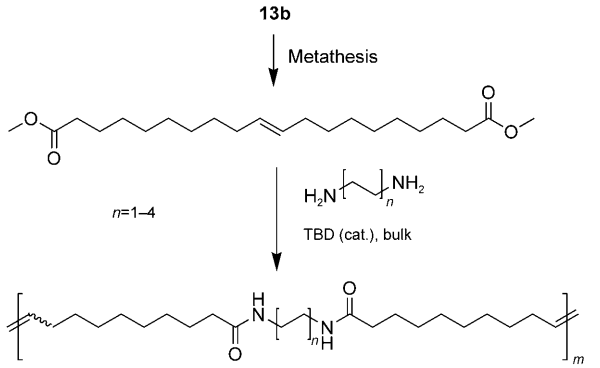
Scheme 16. Products formed from methyl oleate **1b** by a one-pot reaction sequence of cross-metathesis, isomerization, methoxycarbonylation, and transesterification.[126]

Bruneau and co-workers recently investigated the ene–yne cross-metathesis of **1b**, thus introducing 1,3-diene systems to fatty acid derivatives.[127] A sequence of cross-metathesis with ethene and subsequent cross-metathesis with an alkyne was necessary to convert the internal double bond of **1b** into terminal ones prior to the ene–yne cross-metathesis, as the direct cross-metathesis of **1b** with alkynes led only to self-metathesis of **1b**, even at high catalyst loadings. Moreover, some of the above-mentioned reactions (e.g., cross metathesis of **1b** with methyl acrylate) were also investigated with an immobilized version of **C3**.[128] Because magnetic nanoparticles were used as a support for the immobilization, this catalyst was easily separated by a magnet, and it was possible to reuse it several times with sustained activity.

3.3.2. Polymers

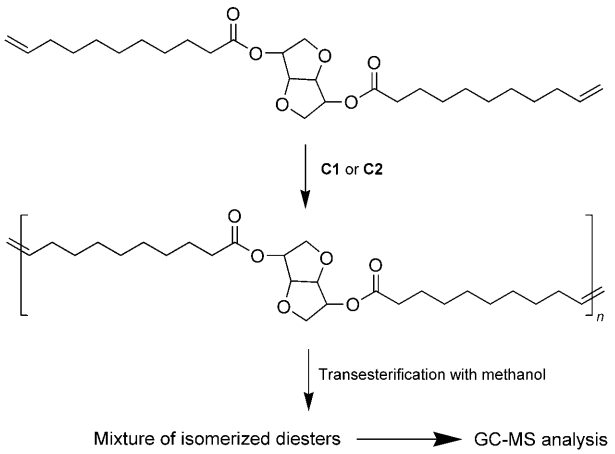
Apart from the described new approaches for the synthesis of monomers and low-molecular-weight platform chemicals from fatty acid derivatives by olefin metathesis, recent examples have also demonstrated the versatility of this renewable feedstock for direct polymer synthesis by olefin metathesis,[101] especially acyclic diene metathesis (ADMET).[129] For instance, the ADMET of 10-undecenyl-10-undecenoate resulted in high-molecular-weight unsaturated polyesters with polyethylene-like structure, and it was possible to prepare telechelics and ABA triblock copolymers with this monomer in a one-step procedure.[130] The ADMET of quite similar amide-containing monomers derived from castor oil, on the other hand, was rather unsuccessful, even when modern functional-group-tolerant catalysts were used.[131] The reason for this disappointing result was the high melting point of these monomers, which make it necessary to polymerize in solution, as the studied catalysts are not stable above 100 °C. The successful strategy to obtain the desired polyamides X,20 is shown in Scheme 17 and relies on the self-metathesis of **13b** and subsequent catalytic amidation with diamines.[131]

A typical problem of ADMET polymerization and other olefin metathesis transformations are olefin isomerization side reactions, especially with second-generation catalysts.[132,133] Such side reactions can easily be quantified for small organic molecules, but their quantification during ADMET polymerizations was only recently described using



Scheme 17. Strategy for the synthesis of polyamides *X*,20 (*X* = 2,4,6,8) from renewable resources by self-metathesis and subsequent catalytic amidation.[131] TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

a monomer from fully renewable resources.[134] Thus, polyesters were prepared under typical ADMET conditions and subsequently transesterified with methanol to be able to analyze and quantify the repeat unit structure by GC-MS (Scheme 18). These studies revealed that highly defined polymers could be obtained with **C1**, whereas **C2** provided rather ill-defined polymeric architectures and showed a temperature-dependent isomerization tendency.[134]

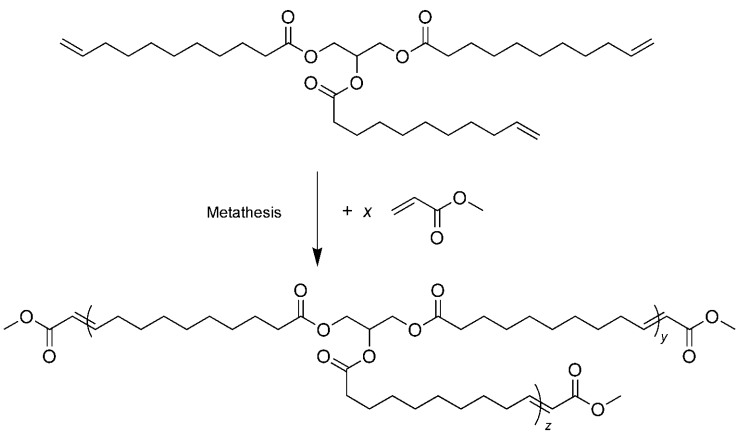


Scheme 18. Strategy for the quantification of isomerization side reactions during ADMET polymerizations.[134]

Subsequently, this quantification method was applied for the optimization of the ADMET reaction conditions with second-generation metathesis catalysts (**C2**, **C3**, and **C4**) in order to obtain as little isomerization with these catalysts as possible.[135] Grubbs and co-workers have shown that 1,4-benzoquinone can prevent double-bond isomerization during the ring-closing metathesis of diallyl ether and other metathesis reactions.[136] This strategy was also successful here, and benzoquinone significantly reduced the number of olefin isomerization side reactions during ADMET polymerizations (leading to less than 10% isomerization with **C3** and **C4**).[135]

Moreover, ADMET polymerizations were used to prepare flame-retardant materials derived from fatty acids by copolymerization of phosphorous-containing monomers.[137,138] A limiting oxygen index (LOI) of 23.5 was obtained for these polyesters from renewable resources with a phosphorous content of only 3.1 %.[137] This value was further improved to a LOI of 25.7 by preparing copolymers with hydroxy functional groups that were functionalized with acrylic acid after polymerization and then radically cross-linked.[138]

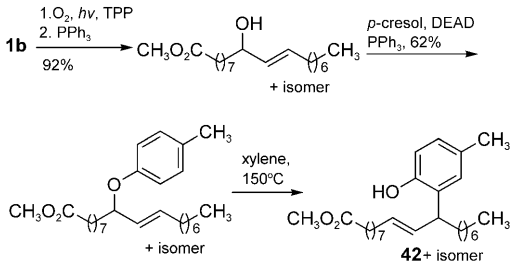
In the first paper of a series on the preparation of resins from plant oils by olefin metathesis, Larock and Tian showed that ADMET polymerizations of soybean oil leads to polymeric materials ranging from sticky oils to rubbers.[139] Interesting materials were also prepared by copolymerization of norbornene-functionalized castor and linseed oils with cyclic monomers.[140–142] Such monomers were also used to prepare resins reinforced with glass fibers, which displayed significantly improved tensile modulus and toughness.[143] Most recently, the ring-opening metathesis polymerization (ROMP) of norbornenyl-functionalized fatty alcohols was studied by the same group. This reaction led to materials with properties that were comparable to petroleum-based plastics such as HDPE and poly(norbornene).[144] However, if model triglycerides and high-oleic sunflower oil were polymerized in the presence of a chainstopper, the cross-linking of the resulting polymers could be completely avoided, and hyperbranched polymers were obtained in a one-step procedure (cf. Scheme 19).[145,146] This type of polymerization was termed acyclic triene metathesis (ATMET) with respect to the monomer functionality, and it was possible to control the molecular weight of these branched polymers by using different amounts of the chainstopper (as expected, the degree of polymerization was lower when higher amounts of the chainstopper were used). Detailed NMR spectroscopy, gel permeation chromatography (GPC), and ESI-MS/MS studies revealed the formation of macrocycles throughout the polymerization, and the identification of oligomers gave detailed information about the polymer architecture as well as the polymerization mechanism.[145,146]



Scheme 19. Preparation of branched polymers by ATMET with triglycerides and chainstoppers.[145]

3.4. C–H Activation

The activation of unreactive C–H bonds in order to introduce functional groups has attracted much attention during the last years.[147,148] In fatty acids, C–H bonds are activated by an adjacent carbonyl group or a double bond. Thus, 2-silylated fatty acid methyl esters were obtained in 19–75 % yield when the fatty acid esters were treated with alkyl silyl triflates and triethylamine or the lithium enolates with chlorosilanes.[149] Allylic bromination with *N*-bromosuccinimide and reaction of the bromides with organocuprates was used for the synthesis of branched methyl oleates,[150] which are of interest as lubricants. The allylic positions of high-oleic sunflower oil triglycerides were also used to obtain reactive α,β-unsaturated ketones by singlet oxygen photoperoxidation.[151] The enone group was subsequently used for cross-linking with diamines by an aza-Michael addition to afford thermosetting polymers. Along the same lines, phenol-substituted methyl oleates have been prepared by photosensitized allylic oxygenation of methyl oleate and subsequent introduction of a phenoxy group and a Claisen rearrangement, to form, for example, **42** (Scheme 20).[152] These fatty



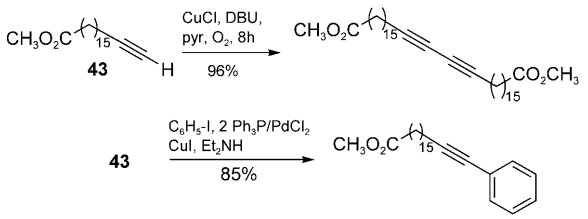
Scheme 20. Synthesis of phenol-substituted methyl oleates (e.g., **42**) by allylic oxygenation. DEAD: diethyl azodicarboxylate, TPP: tetraphenylporphyrin.

acid conjugates are antioxidants whose performance is of the same order as that of α-tocopherol or *tert*-butylhydroquinone.

The C–H bond of alkynes is also reactive and can be selectively substituted. Thus methyl 17-octadecynoate (**43**, prepared from **1b**) can be dimerized at the terminal C–H bond,[153] or the hydrogen atom can be replaced by an aryl group in a palladium-catalyzed substitution (Scheme 21).[154]

4. Enzymatic and Microbial Transformations

The use of enzymes as biocatalysts and of (engineered) microorganisms in the area of fats and oils can be divided into three major areas: 1) the modification of fats and oils already available from renewable resources, 2) the transformation of precursors, such as alkanes, into fatty acids, and 3) the de novo synthesis of fatty acids, fats, or oils from carbon sources such as glucose. Table 2 provides a survey of selected enzymes or microorganisms, their application areas, and examples.



Scheme 21. Oxidative dimerization and arylation of methyl 17-octadecynoate (**43**). DBU: diazabicycloundecene.

Table 2: Microorganism and enzymes used for lipid production and modification.

Enzyme or Microorganism	Application	Examples	Ref.
Lipases	structured triglycerides	cocoa-butter equivalent, betapol	[155–158]
	enrichment/incorporation of specific fatty acids	PUFA from fish oils	[159,160]
	ester synthesis	emollient esters	[161,162]
	biofuels	FAMEs[a]	[163,164]
Phospholipases	removal of fatty acids in *sn*1- or *sn*2-position (PLA_1 or PLA_2)[b]	degumming of oils	[165]
	removal of phosphate groups (PLC)[b]	degumming of oils	[166,167]
	head-group exchange (PLD)[b]	synthesis of phosphatidylserine	[168]
P450-monooxygenases, yeasts such as *Candida tropicalis*	microbial hydroxylation of fatty acids	Precursors for polyesters/lactones, flavor compounds	[169]
Candida bombicola	biosurfactants	sophorolipids	[170]
Pseudomonas sp.	biosurfactants	Rhamnolipids	[171]
marine protists such as *Schizochytrium* sp.	single-cell oils	PUFA (AA, DHA, EPA)[b]	[172]
Mortierella alpina	single-cell oils	AA[b]	[173,174]

[a] FAME: fatty acid methyl ester. [b] PUFA: poly unsaturated fatty acid; AA: arachidonic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; PL: phospholipase.

4.1. Use of Isolated Enzymes

A broad range of enzymes can be used for the conversion of fats, oils, and other lipids, and their application is well-documented in the literature.[175–178] The most important enzymes and the products of the biocatalytic reactions that they catalyze are summarized below.

4.1.1. Application of Lipases

The by far most used biocatalysts are lipases (EC 3.1.1.3, triacylglycerol hydrolases), as fats and oils are their natural substrates. These enzymes do not require cofactors, many of them are available from commercial suppliers, and they exhibit high activity and stability, even in non-aqueous environments. A plethora of publications on the use of lipases has appeared in the last two decades, and only the most important and recent examples are highlighted here. Because lipases show chemo-, regio-, and stereoselectivity, they can be used for the tailoring of natural lipids to meet nutritional demands, especially for humans. The most prominent example is the synthesis of cocoa-butter equivalent (CBE)[155], which is predominantly 1,3-disaturated-2-oleyl-glyceride, where palmitic, stearic and oleic acids account for more than 95% of the total fatty acids. Unilever[156] and Fuji Oil[157] filed the first patents for the lipase-catalyzed synthesis of cocoa butter equivalent from palm oil and stearic acid. Both companies currently manufacture it using 1,3-selective lipases by transesterification or acidolysis of cheap oils using tristearin or stearic acid as acyl donors.

Structured triglycerides (sTAGs) with a defined distribution of different fatty acids are important compounds for a range of applications in human nutrition. sTAGs contain medium-chain fatty acids at the *sn*1- and *sn*3-positions together with a long (preferentially polyunsaturated) fatty acid at the *sn*2-position. They are used, for instance, to treat patients with pancreatic insufficiency as well as for rapid energy supply (i.e., for sports). Another important example is Betapol, which is used in infant nutrition. It contains oleic acid at the *sn*1- and *sn*3-positions and palmitic acid at the *sn*2-position (OPO). The enzymatic production is advantageous over a chemical synthesis, as the regiospecificity and the specificity of fatty acid chain length achieved by lipases can be exploited to generate pure products with desired nutritional properties. Betapol is manufactured by transesterification of tripalmitin with oleic acid using a lipase from *Rhizomucor miehei* (Novozyme RMIM). However, the product contains only 65% palmitic acid in the *sn*2-position.

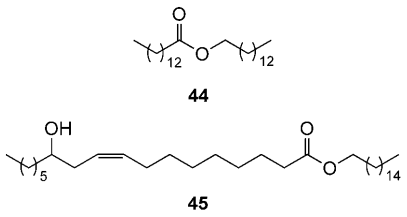
To obtain higher purities and yields of Betapol, a two-step lipase-catalyzed process was developed in which an ethanolysis of tripalmitin with a lipase from *Rhizopus delemar* yields highly pure *sn*2-monopalmitin, which is then esterified by lipase with oleic acid to produce OPO (yield 70%) with up to 96% purity.[158] Another possibility is to start from 1,3-diacylglycerides (1,3-DAGs), which are available on a large scale as cooking and frying oils or can be obtained from glycerol and fatty acid vinyl esters.[179] These 1,3-DAGs can then be esterified with a lipase that exhibits distinct fatty acid selectivity, that is, the lipase must not act on the fatty acids present in the *sn*1- and *sn*3-position and must solely catalyze the introduction of the second type of fatty acid into the *sn*2-position. It could be shown that commercial lipase from *Pseudomonas cepacia* (Amano PS) and *Candida antarctica* (CAL-B) allow for the synthesis of sTAGs owing to their distinct fatty acid specificity.[180] The first lipase-like enzyme with distinct *sn*2-specificity was recently created by directed evolution of an esterase and might open an alternative for the synthesis of these compounds.[181]

Recent examples for successfully industrialized processes are the production of margarines (ADM/Novozymes) without *trans*-fatty acids and of diglyceride-based cooking and

frying oils (Kao Corp./ADM, annual production > 30 000 tons)[182] using a lipase from *Thermomyces lanuginosa* (TLIM).[183] ADM and Novozymes received the Presidential Green Chemistry Challenge Award for these processes in 2005.

The selectivity of lipases has also been explored for the enrichment of polyunsaturated fatty acids such as eicosapentaenoic acid or docosahexanoic acid from fish oil. These ω−3 fatty acids have a variety of positive effects on human health, especially that they reduce the risk of coronary heart disease and lower blood pressure and cholesterol levels. The enzymatic reaction can be performed by hydrolysis, alcoholysis, or selective transesterification, and several processes were commercialized.[159,160] Another important fatty acid is conjugated linoleic acid (CLA) with the *trans*10/*cis*12-isomer as the most important one for human nutrition. A lipase from *Geotrichum candidum* was found to be the best of a number of enzymes to separate this isomer from others formed during chemical isomerization of linoleic acid.[184]

Lipases have also been used on the industrial scale to produce simple esters, for example, for cosmetic applications (Scheme 22). Prominent examples are myristyl myristate (**44**)



Scheme 22. Emollient esters such as myristyl myristate (**44**) and cetyl ricinoleate (**45**) are produced industrially by lipase catalysis.

and cetyl ricinoleate (**45**).[161,162] Although both esters have been chemically synthesized for a long time, enzyme technology allows higher yields and substantially purer products. The higher costs for the biocatalyst are compensated by savings in energy (ambient temperature instead of 160–180 °C) and easier product purification (i.e., a bleaching and deodorization step can be omitted).

The lipase-catalyzed synthesis of fatty acid alkyl esters (FAAEs, predominantly methyl esters) to be used as biodiesel has also been extensively studied.[163,164] Very recently it was reported that the first large-scale biodiesel plant using enzyme technology has started operation in China (capacity 20 000 metric tons per year) using *tert*-butyl alcohol as co-solvent. Still, most lipase-based reactions suffer from the prohibitively high costs of the biocatalysts (despite extensive progress in their protein engineering),[185] and the majority of biodiesel is still produced by chemical means.[186] One niche is the enzymatic FAME production from waste frying oils or oils with high content of free fatty acids or water, where the chemical catalyst can be deactivated or yields are unsatisfactory. The enzymatic utilization of the by-product glycerol from biodiesel production is covered in detail in a review.[178] A very recent example is the lipase-catalyzed synthesis of amphiphilic esters starting from mannitol or sorbitol using fatty acid vinyl esters as acyl donors. The products have been shown to be useful as phase-selective gelators, for example as solidifiers for oil spills.[187]

4.1.2. Application of Phospholipases

Phospholipases are divided into four groups (PLA_1, PLA_2, PLC, and PLD), depending on their site of action on the phospholipid molecule. PLA_1 and PLA_2 are used on large scale for degumming (the removal of phospholipids) of natural fats and oils.[165] Whereas earlier processes used a mammalian phospholipase from the porcine pancreas specific for the *sn*2-position (PLA_2), this method was replaced by an enzyme obtained from *Fusarium oxysporum*, which exhibits *sn*1-selectivity (PLA_1). More recently, a chimeric enzyme was created by protein engineering from a lipase scaffold and parts of the *Fusarium* enzyme.[165] The action of the enzymes releases lysophospholipids, which are easily hydrated and therefore allow the reduction of the phospholipid content to less than 10 ppm. An alternative approach is the use of PLC as introduced by Verenium Corp., which generates a 1,2-DAG and the phosphate residue bearing the headgroup.[166,167,188,189] This process has the advantage that no oil loss occurs, and the removal of the phosphate is claimed to be as efficient as with PLA_1 or PLA_2. Phospholipase D can be used for a head-group exchange. This procedure enables the synthesis of non-natural phospholipids as well as of compounds bearing natural head groups, such as phosphatidyl serine, which are reported to have positive effects on brain function.[168]

4.2. Microbial Transformations

Microbial biotransformations are especially useful for multistep conversion of triglycerides, fatty acids, or alkanes and the de novo synthesis of lipid products. In the case of oxidoreductases, whole cell systems are preferred, as the enzymes display low stability and turnover rates and require cofactors. One example is lipoxygenases catalyzing the dioxygenation of PUFAs bearing a *cis*-1,4-pentadiene unit to conjugated hydroperoxydienoic acids, which lead, in combination with other enzymes, to the formation of aldehydes such as hexanal that are useful for the aroma industry.[190] Of high industrial relevance is the terminal oxidation of carboxylic acids or alkanes catalyzed by P450 monooxygenases of the CYP52 family in combination with alcohol oxidases and aldehyde dehydrogenases.[169,191] The ω-hydroxy fatty acids produced as intermediates are also of interest, for example as lactone precursors.[192]

The microbial production of wax esters has also been described. The key enzyme is a bifunctional wax ester synthase/acyl-CoA:diacylglycerol acyltransferase from *Acinetobacter calcoaceticus* ADP1, which catalyzes the condensation of a fatty acid and a long-chain alcohol to form wax esters such as jojoba oil.[193] The potential of this enzyme, which can be expressed recombinantly in *E. coli*, for the production of oleochemicals and biofuels has recently been proposed.[163,194,195]

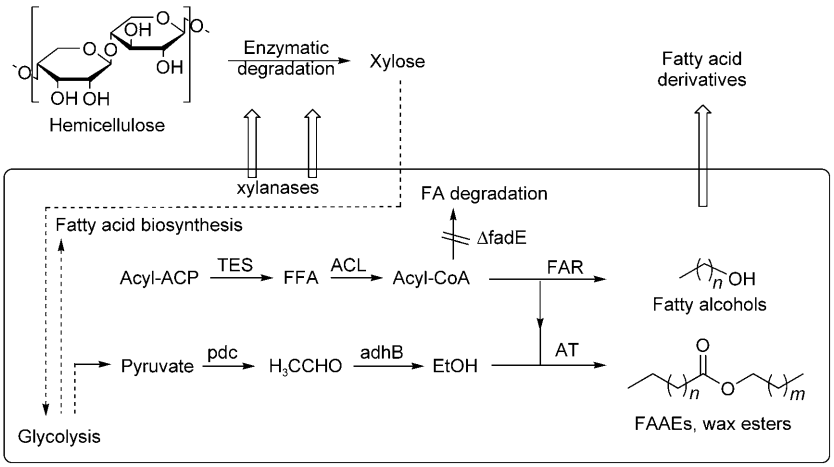
Other important microbial products are biosurfactants, of which sophorose and rhamnolipids as the most prominent examples.[196] Their surface-active properties are comparable to chemically derived surfactants, but they are biodegradable and obtained from renewable resources. Both lipids are already manufactured on an industrial scale.[178] The highest productivity of 400 $g L^{-1}$ was reported for the yeast *Candida bombicola* utilizing glucose and seed oils such as soy bean or canola oil, but whey[170] or waste fatty acids[171] can also be used as precursors. Other important microorganisms are *Pseudomonas* sp. and *Ustilago* sp. With increasing understanding of the pathways involved in the biosynthesis of these lipids,[197,198] genetic modification to tailor specific product structures and further enhance productivities is already underway.

An alternative to the lipase-catalyzed enrichment of PUFAs from fish oil (section 4.1) is the direct production of these fatty acids as single-cell oils. Several microorganisms, mainly of marine origin, are able to perform the biosynthesis of EPA ($C_{20:5}$), DHA ($C_{22:6}$), or even the ω−6 fatty acid arachidonic acid (AA, $C_{20:4}$), presumably using polyketide synthase pathways.[172] The production of these fatty acids has already been commercialized by several companies.[178] Another relevant microorganism is *Mortierella alpina*, which can accumulate up to 70 % AA of its total fatty acid content.[173,174]

4.3. Metabolic Engineering and Synthetic Biology

Genetic manipulation of key enzymes to enhance the production of certain fatty acids or lipid-related products in microorganisms, for example in the formation of biosurfactants,[197,198] ω-dicarboxylic acids,[199] or fatty acid ethyl esters,[194,195] has already been shown. A promising avenue for new processes takes advantage of the major achievements in metabolic engineering and synthetic biology fostered by the vast amount of genome and protein sequence data. This approach opens access to alternative production routes not only for chemicals such as 1,3-propane diol,[200] succinic acid, or 3-hydroxypropionic acid, but also for fatty acids, alkanes, and biofuels derived from them.[201–204] The major driving force is the development of sustainable routes for biofuel production, with bioethanol as the most prominent example utilizing *E. coli* or *Saccharomyces cerevisiae* as standard hosts. In addition to efficient pathway manipulations, cheap, abundant, and easy-to-metabolize starting materials as well as the recovery of the products are key issues to make such processes cost-efficient.

The currently most advanced example is the engineering of *E. coli* to produce structurally tailored fatty acid ethyl esters (FAEE), fatty alcohols, and wax esters from simple sugars, including the utilization of hemicelluloses derived from plant biomass.[205] The keys to direct production of FAEE were cytosolic expression of a thioesterase, control of fatty acid chain-length profile by introduction of plant-derived enzymes, elimination of several side reactions to deregulate fatty acid biosynthesis, coexpression of a wax ester synthase, and ethanol formation from pyruvate (Scheme 23).



Scheme 23. Engineered pathways for production of FAAEs, fatty alcohols and wax esters in *E. coli*. Overexpression of thioesterases (TES), acyl-CoA ligases (ACL), and deletion of β-oxidation (ΔfadE) lead to enhanced free fatty acid (FA) production. ACP: acyl carrier protein, FAR: fatty acyl CoA reductase, AT: acyl transferase, pdc: pyruvate decarboxylase, adhB: alcohol dehydrogenase.

Furthermore, fatty alcohol production was achieved by introduction of two reductases.

The yields reported (up to 674 $mg L^{-1}$ FAEE, 9.4 % of theoretical yield) are reported to be only one order of magnitude below that required for commercial production. It can be expected that further improvements in combination with process development will soon enable the production of FAEE and derived products in these engineered microorganisms.

5. Summary and Outlook

It can be expected that the observed geographical and feedstock shift of oleochemical production from North America and western Europe to southeast Asia and from tallow to palm oil will continue during the next decade. The fatty acids of bulk oils used in current oleochemistry are rather uniform. It will be important to introduce and to cultivate more and new oil plants containing fatty acids with interesting desired properties for chemical utilization by using the huge diversity of plant seed oils. The simultaneous increase in agricultural biodiversity presents a real challenge for plant breeders. The problem of the industrial utilization of food plant oils, which has become more urgent with the development of the global biodiesel production, could be solved by a scenario of cultivation of appropriate oil plants on degraded land, which would not compete with agricultural food production. Thus, sustainable biodiesel could be sup-

plied not only as a fuel but also as a potential feedstock for the chemical industry. In the context of biofuels, it is also worth noting that catalytic routes to deoxygenated fatty acid derivatives might be of future importance for biodiesel with improved performance.[206]

Important advances have been made in the execution of selective reactions across the double bond and in the exploitation of the chiral pool of fatty compounds. A genuine breakthrough is the ω-functionalization of fatty acids containing internal double bonds to give, for example, α,ω-dicarboxylic acids by methoxycarbonylation. The application of the olefin metathesis reaction for the synthesis of ω-functionalized fatty acids as well as for direct polymer synthesis has become and will remain a hot topic. The complete series of linear dicarboxylic acids and the corresponding diols and diamines as well as ω-hydroxy and ω-amino fatty acids with a chain length from C_6 to longer than C_{20} have thus become available.[207] These compounds will be used in the coming years as substrates for the synthesis, and, hopefully, production of a great variety of polyesters, polyamides, and polyurethanes. The first results on copolymerization of alkenes and ω-unsaturated fatty acids give evidence for completely new utilizations of fatty compounds. Moreover, the use of enzymes and microorganisms for the modification of fats and oils, the transformation of precursors, for example, oleic acid into *cis*-octadec-9-enoic diacid, and the de novo synthesis of fatty acids from abundantly available renewable carbon sources have made and will continue to make fascinating advances.

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