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Aims and Scope

The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry. As our understanding of organometallic structures, properties and mechanisms grows, new paths are opened for the design of organometallic compounds and reactions tailored to the needs of such diverse areas as organic synthesis, medical research, biology and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry, where new breakthroughs are being made that are of significance to a larger scientific audience.

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Preface

Growing scarcity of fossil resources, concerns about the effects of global warming, and the desire for a more independent, stable supply of energy and resources force us to develop more sustainable production routes based on renewable resources. These efforts should culminate in the development of highly integrated biorefineries, which will eventually replace the conventional petrochemical ones. In order to be able to compete economically as well as ecologically, such biorefineries should not only produce our required energy-carriers but also focus on the production of high value chemicals and materials, as needed by our society, to be an integral part of such a facility. As far as the renewable production of carbon-containing chemicals and liquid transportation fuels is concerned, biomass is in principle the only viable and abundantly available alternative resource. This, of course, with the provision that the biomass is produced in such a manner that it does not compete with the food supply.

In addition to the geopolitical imperative for a transition from fossil to renewable resources, using biomass as feedstock holds additional, specific advantages for the chemist. Nature supplies us with an enormous structural diversity in the highly functionalized feed that is biomass. Not only are the various components of biomass often extensively functionalized, they often come to us stereochemically pure. This feedstock thus provides an excellent opportunity for a more facile production of highly valuable polymer building blocks, specialty chemicals and pharmaceuticals. Indeed, achieving such structural complexity in the petrochemical bottom-up approach by selectively introducing functional groups, hetero-atoms, and stereochemical information is currently a rather cumbersome process as one has to start from non-functionalized hydrocarbons. For the production of bulk and commodity chemicals, on the other hand, selective defunctionalization is often required if we want to obtain these high volume products from renewable resources. In any case, i.e., both for selective functionalization as well as defunctionalization, the development of new catalysts and new catalytic conversion routes will be essential. In fact, catalysis has been identified as one of the key enabling technologies ultimately required for the realization of the "ideal biorefinery." To achieve this, both chemical and enzymatic catalysis will be necessary and in particular a combination of both represents a promising yet challenging approach. Organometallics, or more broadly speaking transition-metal complexes, are ideally suited as catalyst to deal with the complex biomass feedstock in a selective manner. One can easily envisage that the application of the general approach of systematic catalyst optimization by rational ligand design, common in transition metal-complex catalysis, to renewable substrates, such as sugars, terpenes, or fatty acid derivatives, can give rise to many new or improved chemo-, regio-, and enantioselective conversion routes. This volume reviews and highlights some of the recent efforts in this direction. The five chapters are organized along the lines of reaction types rather than class of renewable substrate. Behr and Vorholt, for instance, discuss a classical set of olefin addition reactions, i.e., the hydroformylation and related conversions, when applied to renewables. The exploitation of unsaturations in renewable substrates such as fatty acids and terpenes by the exceptionally versatile ruthenium-metathesis catalysts is reviewed by Montero de Espinosa and Meier. Korstanje and Klein Gebbink review the wealth of information on the selective rhenium-catalyzed oxidation and deoxygenation of renewables. Bruijnincx, Weckhuysen, and co-workers discuss the renaissance of the palladium-catalyzed telomerization reaction in light of the recent use of renewables as multifunctional substrates. Finally, Williams and co-workers show the recent advances in using transition-metal catalysts and initiators for the production of renewable polymers. Together, these contributions show the potential and power of using transition-metal catalysts for the production of renewable chemicals. One also has to note, however, that the area of “Organometallics and Renewables” is a terrain that largely still remains to be explored. Many other exciting contributions of research on catalysis with organometallics to the blooming field of catalytic biomass conversion can therefore be expected in the near future. We hope that this volume not only highlights the potential of the field but also serves as a source of inspiration for the organometallic chemist to further investigate this field rich in opportunities.

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Olefin Metathesis of Renewable Platform Chemicals

Lucas Montero de Espinosa and Michael A. R. Meier

Abstract Olefinic double bonds are often found in the structure of natural compounds. This makes olefin metathesis a powerful tool for their transformation into valuable renewable platform chemicals and, in some cases, directly for targeted chemical products. Natural products display many different structures and functional groups, which in some cases challenge catalyst performance. In this respect, new catalysts with improved performance are constantly developed providing new application possibilities. This chapter covers the research performed in the field of olefin metathesis with renewable chemicals, starting from the early days of this chemical reaction to the present situation. Special attention is given to renewables naturally containing double bonds, like oleochemicals or terpenes. On the other hand, the introduction of double bonds in the structure of non-olefinic renewables, such as carbohydrates, amino acids, or peptides, and their use as olefin metathesis substrates are discussed. This chapter is subdivided in two main parts covering the synthesis of platform chemicals and the synthesis of polymers, respectively.

Keywords Amino acids • Carbohydrates • Olefin metathesis • Plant oils • Platform chemicals • Polymers • Renewables • Terpenes

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1 Introduction

Among the existing reactions leading to formation of covalent bonds, those generating new carbon–carbon bonds are of utmost importance for organic chemistry. In this respect, and beyond classical organic reactions, transition metals provide a rich chemistry for synthetic chemists. Among the different metal-catalyzed carbon–carbon bond forming reactions, olefin metathesis is one of the most powerful, straightforward, and versatile. The history of olefin metathesis is full of highlights, from the initial observations of double-bond scrambling back in the 1950s, and the establishment of the accepted mechanism in 1971, to the present situation with countless application possibilities. The impressive advance that olefin metathesis has experienced in the last decades has been possible due to detailed mechanistic studies that, eventually, permitted the development of catalysts for almost every possible synthetic problem. Olefin metathesis reactions are mainly classified as ring-opening metathesis (ROM), ring-closing metathesis (RCM), self-metathesis (SM), cross metathesis (CM), ring-opening metathesis polymerization (ROMP), and acyclic diene metathesis (ADMET) polymerization. These reactions are illustrated in Fig. 1.

The first examples of metathesis-related research were reported in the late 1950s and early 1960s by researchers at DuPont, Standard Oil, and Philips Petroleum. Anderson and Merckling described the polymerization of norbornene in the presence of $TiCl_4$ and a reducing agent [1], although the polymerization mechanism remained unknown. Shortly after, Eleuterio reported the polymerization of cyclic olefins by metal oxides such as chromium, tungsten, uranium, and most successfully molybdenum oxide supported on titania, zirconia, or alumina [2]. Simultaneously, Truett, Johnson, Robinson, and Montague proposed the structure of polynorbornene produced in the presence of $TiCl_4$ and different lithium aluminum tetraalkyls [3], and some time afterward, Banks and Bailey observed the formation of ethylene and 2-butenes when propene was heated with $[Mo(CO)_6]$, $[W(CO)_6]$, and MoO_2 supported on alumina [4]. These results suggested that a new reaction was taking place in which two olefins were disproportionated, forming two new olefins. In 1967, Calderon and coworkers recognized that both the ring-opening polymerization of unsaturated alicyclic compounds [5] and the disproportionation of acyclic olefins [6] in the presence of tungsten hexachloride and ethylaluminum dichloride were the same reaction and named it “olefin metathesis” (from Greek,

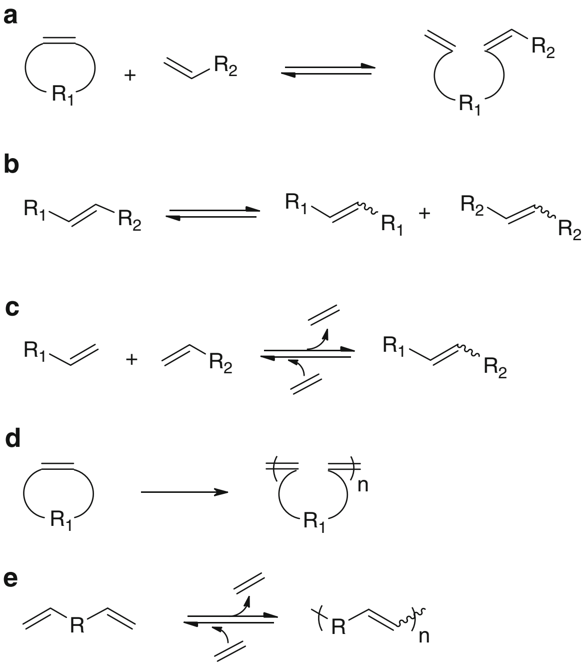


Fig. 1 Olefin metathesis reactions: (**a**) ring-opening metathesis (ROM) and ring-closing metathesis (RCM), (**b**) self-metathesis (SM), (**c**) cross metathesis (CM), (**d**) ring-opening metathesis polymerization (ROMP), and (**e**) acyclic diene metathesis (ADMET) polymerization

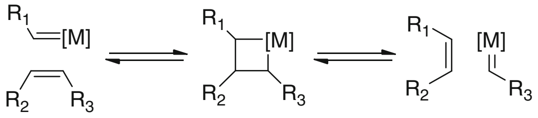


Fig. 2 Mechanism of olefin metathesis proposed by Hérisson and Chauvin in 1971 [7]

changing or exchanging positions). The mechanism, however, was described by Hérisson and Chauvin in 1971, who proposed that a metal alkylidene and a metallacyclobutane were the intermediates of the olefin metathesis reaction (Fig. 2) [7]. This mechanism is still accepted today.

The proposed idea that metal alkylidene complexes are be able to catalyze olefin metathesis was confirmed in 1980 [8] and consolidated in 1986 by Schrock with the development of the first well-characterized, highly active, neutral tungsten (**C1**, Fig. 3) [9] and molybdenum (**C2**) [10] alkylidene complexes. These complexes were able to catalyze both the metathesis of different olefins and the ROMP of functionalized norbornene to polynorbornene with low polydispersities [11]. Moreover, these catalysts were used by Wagener and coworkers to perform the first quantitative ADMET polymerization [12] and copolymerization [13] of 1,5-hexadiene and 1,9-decadiene. However, the low stability of these catalysts in

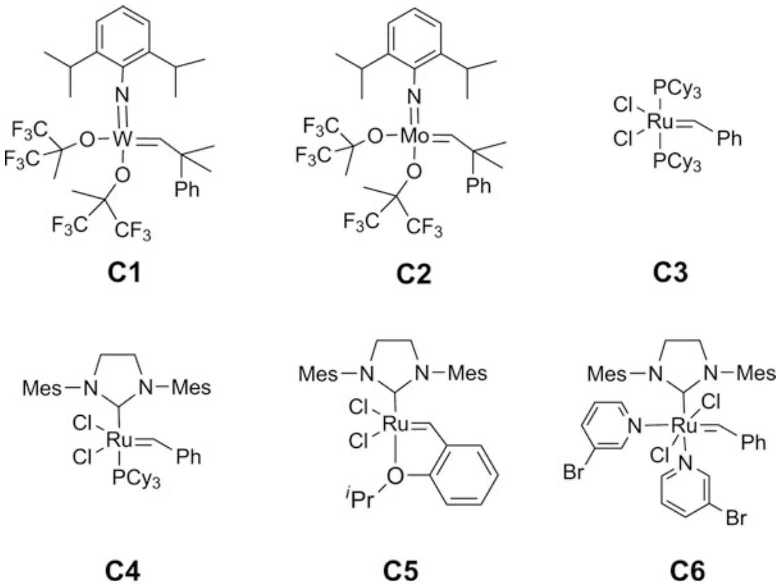


Fig. 3 Olefin metathesis catalysts: Schrock tungsten (**C1**) and molybdenum (**C2**) alkylidene complexes, Grubbs first- (**C3**) and second-generation (**C4**) catalysts, Hoveyda–Grubbs second-generation catalyst (**C5**), and Grubbs third-generation catalyst (**C6**)

combination with their limited functional group tolerance was still a major drawback. In this regard, key to the development of olefin metathesis was the synthesis of the first well-defined ruthenium alkylidene complex by Grubbs in 1992 [14]. This carbene species was able to catalyze the ROMP of norbornene both in the absence and presence of protic or aqueous solvents, representing an important advance toward the applicability of the olefin metathesis reaction. Subsequent investigations led to the synthesis of the well-known, air stable, and commercially available Grubbs first-generation catalyst (**C3**) [15], which expanded the scope of olefin metathesis to substrates bearing different functional groups [16]. However, **C3** presents low stability toward some functional groups such as aldehydes, alcohols, or carboxylic acids. In 1998, Herrmann reported that the introduction of *N*-heterocyclic carbenes (NHCs) as ligands improved the functional group tolerance of ruthenium-based metathesis catalysts [17]. This finding eventually led to the development of a second generation of ruthenium alkylidene complexes with improved metathesis activities, which are also commercially available and widely used as the Grubbs (**C4**) [18] and Hoveyda–Grubbs (**C5**) [19] second-generation catalysts. The improvement of metathesis catalysts has continued since then, and nowadays many different catalysts exist with activities that are tuned toward a variety of specific applications. Among others, and in relation with this chapter, it is worth to mention the Grubbs third-generation catalyst (**C6**) [20]. This catalyst is very efficient in the ROMP of a number of monomers, displaying both high activity and very fast initiation, thus leading to low-polydispersity polymers [21].

Apart from the development of new catalysts, the examples of application of olefin metathesis in the literature are uncountable, including total synthesis, polymer, and

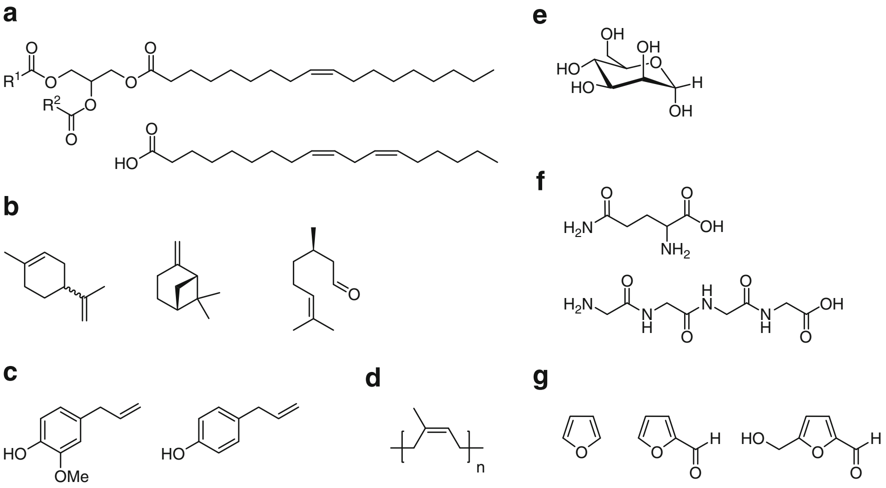


Fig. 4 Renewable platform chemicals used in olefin metathesis: (**a**) plant oils and fatty acids, (**b**) terpenes and terpenoids, (**c**) phenylpropanoids, (**d**) natural rubber (*cis*-1,4-polyisoprene), (**e**) carbohydrates, (**f**) amino acids and peptides, and (**g**) furans

material sciences, among others. The application of olefin metathesis to renewable raw materials, either directly or after modifying them, is an active field that grows in parallel to the development of new metathesis catalysts of improved activity and functional group tolerance. The use of renewable platform chemicals for olefin metathesis is justified not only because of environmental issues but also because of the enormous potential that these raw materials possess. Double bonds are widely found in plant oils, fatty acids, terpenes, lignin-derived products, natural rubber, and others. Moreover, renewable raw materials have very different chemical structures, from aliphatic to cyclic and aromatic, giving rise to different synthetic possibilities and allowing for the preparation of materials with designed properties.

Among all renewable raw materials, plant oils are the most attractive playground for olefin metathesis (Fig. 4a). A wide variety of unsaturated fatty acids and esters, which are industrially obtained via saponification and transesterification of plant oils, are available as renewable platform chemicals. Natural fatty acids contain isolated or conjugated internal double bonds and, in some cases, alcohol or epoxide groups. However, terminal olefins are preferred in olefin metathesis since ethylene can be easily removed, thus driving the reaction to completion. For this reason, 10-undecenoic acid, which can be obtained by pyrolysis of ricinoleic acid at temperatures over 350°C, is of special interest for this chapter [22–24]. Plant oils (triglycerides) can be used directly or after different modifications for olefin metathesis to obtain cross-linked polymers. On the other hand, fatty acids and esters are excellent starting materials for the synthesis of a variety of building blocks and monomers via olefin metathesis. Furthermore, α,ω-dienes derived from 10-undecenoic acid are perfect monomers for ADMET polymerization.

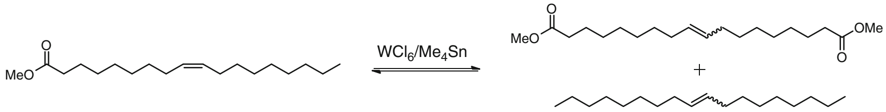
Another class of renewable compounds presenting suitable structures for the application of olefin metathesis is represented by terpenes (Fig. 4b). This highly diverse family of compounds has the isoprene unit as a common structural feature, which leads to characteristic internal and/or terminal double bonds. Most common terpenes like α-pinene, β-pinene, or limonene are produced abundantly by many types of plants and used industrially in the production of fragrances and flavors. Moreover, less common terpenes and terpenoids such as carene, citral, citronellal, citronellol, or geraniol offer different structures and functional groups in addition to the double bonds. Another interesting family of compounds found in the plant kingdom is phenylpropanoids (Fig. 4c), having an aromatic ring substituted with a propene chain as common structural motif. Members of this class of compounds are eugenol, chavicol, or estragol, in which the phenyl ring is an added value to their potential as substrates for olefin metathesis. Furthermore, natural rubber (*cis*-1,4-polyisoprene, Fig. 4d) is an abundant unsaturated polymer and thus suitable for a number of transformations via olefin metathesis.

Furthermore, although not naturally containing double bonds, carbohydrates (Fig. 4e), amino acids, and peptides (Fig. 4f) can be chemically modified by introduction of olefins in their structure. The chemistry of these natural compounds represents different branches of organic chemistry, and a full review of olefin metathesis-related transformations of such compounds is out of the scope of this chapter. However, some examples will be discussed taking into account the interesting properties that these compounds provide, like in the case of glycopolymers [25]. Another interesting family of compounds, which can be derived from carbohydrates, is furans (Fig. 4g). Furan is industrially obtained by the palladium-catalyzed decarbonylation of furfural, which in turn is obtained from the acid-catalyzed depolymerization and dehydration of xylan, a plant-derived polysaccharide [26, 27]. The global production of furfural is around 300,000 tons per year, being mainly employed in the synthesis of furfuryl alcohol [25]. Furans themselves do not participate in olefin metathesis; however, they can be easily transformed through Diels–Alder cycloadditions into 7-oxabicyclo[2.2.1]hept-5-ene derivatives, which are suitable monomers for ROMP [28]. Furans are thus renewable building blocks for the synthesis of monomers of diverse structures, depending on both the furan and the dienophile used. Finally, as general selection criteria of the examples discussed in this chapter, we focus only on those in which the olefin functionality is introduced in few synthetic steps.

2 Synthesis of Platform Chemicals

2.1 Plant Oils and Fatty Acids

The application of olefin metathesis to fatty acids and related compounds has its starting point in 1972 with the selective transformation of methyl oleate into equimolar amounts of 9-octadecene and dimethyl 9-octadecene-1,18-dioate by Van Dam, Mittelmeijer, and Boelhouwer (Scheme 1) [29]. In this early work, 1–2 mol% of a



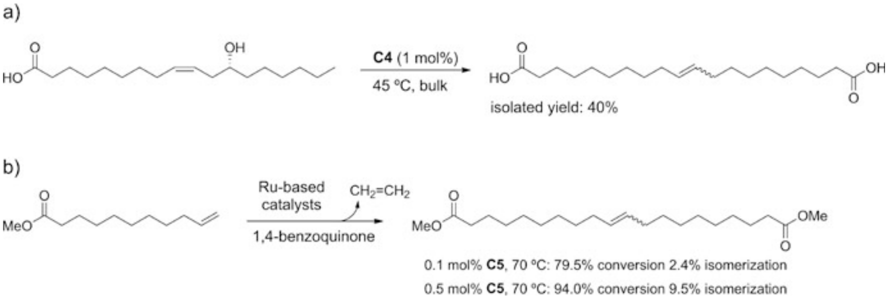
Scheme 1 SM of methyl oleate catalyzed by WCl_6/Me_4Sn [27]

catalytic system consisting of WCl_6/Me_4Sn was used, reaching equilibrium conversion within 4 h at 70°C. Through this method, a new rapid access to α,ω-diesters was disclosed, which are potentially useful for the synthesis of polyesters and polyamides. Moreover, in the following years, the olefin metathesis of oleochemicals was also applied to the synthesis of surfactants or natural products [30].

2.1.1 Self-Metathesis

Concerning SM, Verkuijlen and Boelhouwer continued the work with investigations on the metathesis of polyunsaturated fatty esters [31]. Linoleic and linolenic esters were reacted in the presence of WCl_6/Me_4Sn, yielding a mixture of alkenes and cycloalkenes together with a remarkable 20 mol% of 1,4-cyclohexadiene. The same catalytic system was later applied by Nicolaides et al. in the SM of a mixture of fatty esters obtained from South African sunflower oil [32]. The reaction rate of linoleate was shown to be higher than that of oleate in accordance with the higher number of double bonds of the former. Heterogeneous catalytic systems have also been used for the SM of oleochemicals [33]; however, they are out of the scope of this chapter.

The development of the above-mentioned first homogeneous ruthenium-based catalysts by Grubbs and coworkers widened the application possibilities of olefin metathesis [14, 15]. These catalysts, in contrast to the previously used tungsten and rhenium catalysts, tolerate many functional groups. Thus, Grubbs and Nguyen [34, 35] reported the SM of methyl oleate in the presence of the ruthenium-based alkylidene complex $Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2$ in dichloromethane, reaching the equilibrium at a conversion of 48%. Moreover, the SM of oleic acid was also performed in the same conditions with 42% conversion leading to a mixture of 1,18-octadec-9-enedioic acid and octadec-9-ene, showing the stability of this catalyst toward the carboxylic acid. Although the introduction of these catalysts is an improvement in terms of both catalytic activity and stability, the laborious syntheses of these ruthenium-based alkylidene complexes represented a drawback to their applicability and motivated investigations on more convenient ruthenium catalyst systems. In this context, Nubel and Hunt showed that a catalyst system comprised of $RuCl_3$/ethanol, a phosphine, and an alkyne, which leads to in situ formation of the Ru-alkylidene, catalyzed the SM of methyl oleate. Conversions of 13–17% were obtained after 4 h at 80–90°C with a catalyst loading of 0.02 mol% [36]. Nevertheless, the appearance of **C3** clearly showed the potential of ruthenium-based alkylidene metathesis catalysts and, indeed, highly influenced olefin



Scheme 2 SM of (**a**) ricinoleic acid [37] and (**b**) methyl 10-undecenoate [39]

metathesis research. This is reflected in numerous following studies, not only in SM, but also in CM of oleochemicals with a wide variety of metathesis partners, ethylene being one of the most relevant in the so-called ethenolysis process.

As a continuation of these investigations, Buchowicz and Mol reported the SM of methyl oleate, erucate, and elaidate in the presence of **C3** [37]. The reactions proceeded in dichloromethane and dichloroethane solutions at 20–80°C, leading to a high selectivity toward the primary metathesis products (up to 96%), and with conversions ranging from 36% to 54% when 0.2 mol% of catalyst was used. **C4** was also shown to catalyze the SM of methyl oleate in ~45% conversion, exhibiting a turnover number (TON) of 440,000 at an impressively low catalyst loading (0.0001 mol%) [38]. Later on, the same catalyst was found to effectively catalyze the solvent-free SM of free fatty acids [39]. Oleic, erucic, 10-undecenoic, and 11-eicosenoic acids of varying purity (from 90% to 99%) were reacted with a catalyst loading of 0.1 mol%, reaching conversions between 74% and 87%. Interestingly, the same conditions worked for the SM of ricinoleic acid, giving a conversion of 63% despite the alcohol functionality (Scheme 2a). Furthermore, these reactions were conducted at catalyst loadings as low as 0.005 mol%, and TONs as high as 10,800 could be obtained.

As already mentioned, the development of metathesis catalysts that can be easily accessed from simple precursors is necessary if a large-scale application is desired. With this in mind, Forman et al. developed a robust ruthenium-based phoban-indenylidene complex through a simple and relatively inexpensive procedure, if compared to the preparation of **C3** [40]. This ruthenium alkylidene was tested in the bulk SM of methyl oleate. As a result, they could reach up to 50% conversion with 0.005 mol% catalyst at 50°C.

The performance of **C3**–**C5**, and the Zhan catalyst (structure in Scheme 6) in the SM of methyl 10-undecenoate was compared by Meier et al. [45]. Loadings between 0.1 and 1 mol% were tested at 50 and 70°C, observing higher conversions (over 96%) for the second-generation catalysts, if compared to **C3** (67–87%). However, also higher degree of double-bond isomerization was observed in the case of second-generation catalysts (55–90%), if compared to **C3** (below 17%). Furthermore, 1,4-benzoquinone was used to suppress olefin isomerization side reactions in the metathesis reactions catalyzed by second-generation catalysts (Scheme 2b) [46]. The addition of 2 mol equivalents of 1,4-benzoquinone (to catalyst), thus, also caused a clear drop in the isomerization degrees down to 1–10% at 50°C and to 20–50% at 70 and 90°C, respectively.

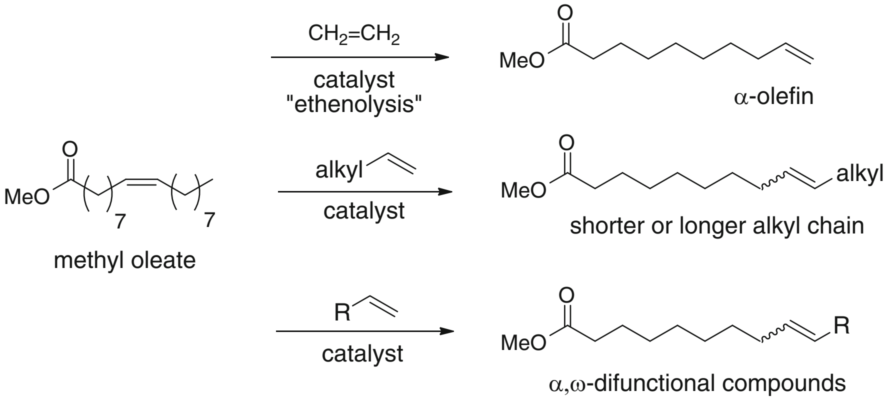
The SM of methyl oleate has been performed by Yinghuai et al. using **C5** immobilized on the surface of modified magnetic nanoparticles [47]. The catalyst was well dispersed in the reaction mixture, producing a quasi-homogeneous catalytic system (0.05 mol% of Ru). The reaction was performed in bulk and gave an isolated yield of 73%. The catalyst was recovered from the reaction mixture using an external magnet and was used for up to five more runs without activity loss.

Another interesting castor oil-derived platform chemical is 10-undecenal, which is at the same time a challenging substrate for olefin metathesis. For the SM of 10-undecenal, Dixneuf et al. modified **C3** and **C5** by insertion of $SnCl_2$ into one Ru–Cl bond [48]. Modification of **C3** led to a binuclear complex, which showed a conversion of 70% at a catalyst loading of 0.33 mol%. On the other hand, both the modified and unmodified **C5** gave conversions over 70% with catalyst loadings of 1.25 mol%, but also led to formation of a high amount of by-products.

2.1.2 Cross Metathesis

The CM of fatty acid esters with alkenes provides a direct route to fatty acid esters of different chain length, if simple olefins are used, and to difunctional products when functionalized olefins are used (Scheme 3). The first report on the CM of oleochemicals described the metathesis of methyl oleate with 3-hexene at 60°C in the presence of the already mentioned catalytic system WCl_6/Me_4Sn [27, 49]. The conversion varied from 20% to 33%, and 3-dodecene and methyl 9-dodecenoate were obtained. In this way, the concept of using olefin metathesis to shorten long-chain fatty esters was proven by obtaining chain lengths in the range of C_{10}–C_{14}, which are the preferred chain lengths for the preparation of detergents. Regarding the first use of functional olefins as CM partners, Kohashi and Foglia studied the reaction of methyl oleate with dimethyl-3-hexenedioate in the presence of 10 mol% of WCl_6/Me_4Sn [50]. They could reach a yield of CM products of 47% after 21 h at 100°C. Moreover, this homogeneous system outperformed the heterogeneous catalytic system $Re_2O_3/Al_2O_3/Me_4Sn$, both in yield of products and reaction rate.

The metathesis of oleochemicals in the presence of ethylene, also called ethenolysis, provides an efficient way to α-olefins and ω-unsaturated esters, which are useful intermediates for the synthesis of polymers, fragrances, surfactants, lubricants, and others [51, 52]. The ethenolysis of methyl oleate was demonstrated in 1994 by Grubbs et al. using **C3** [32]. They could reach productive turnovers of 130–140. In 2001, Warwel et al. carried out the ethenolysis of the methyl esters of oleic, erucic, 5-eicosenoic, and petroselinic acids also in the presence of **C3** [53]. The reactions were performed at 50°C and 10 bar using 0.025 mol% of catalyst and gave conversions from 58% to 74%.

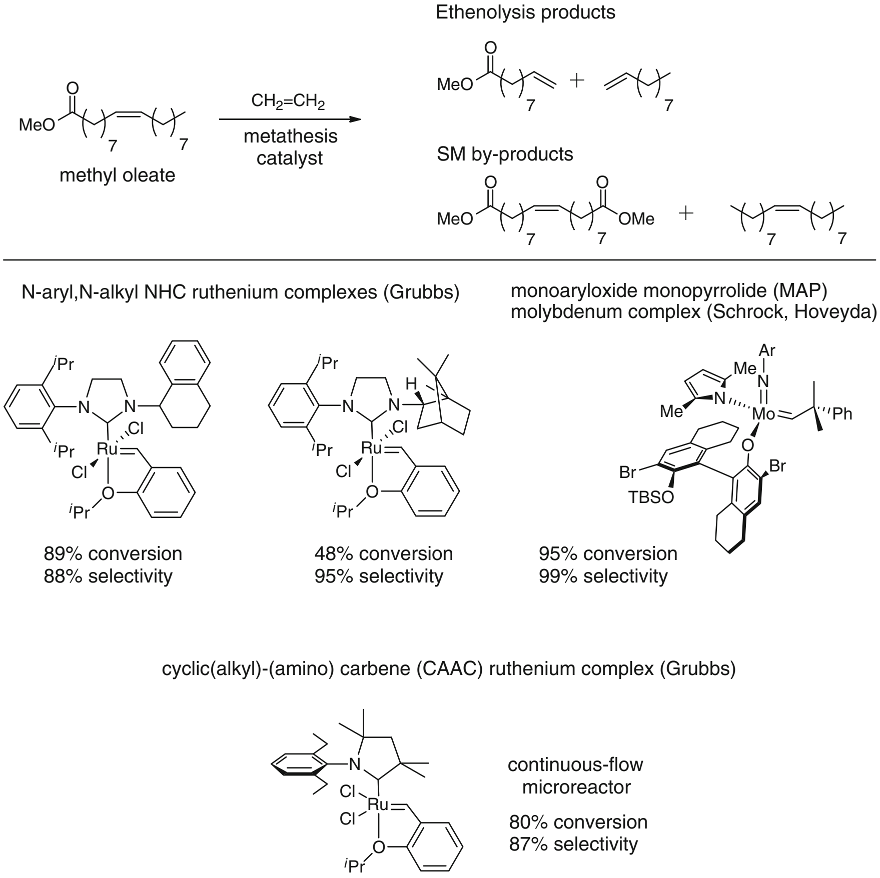


Scheme 3 Access to fatty ester derivatives via CM of methyl oleate with ethylene (ethenolysis), nonfunctional olefins, and functional olefins

One of the main issues of the ethenolysis reaction is the reactivity loss at high conversions of substrate, which limits its commercial viability. Maughon et al. investigated on the mechanism of the ethenolysis of methyl oleate at 25°C, 5.2 bar of ethylene, and in the presence of **C3**, in order to gain insight into the reasons for these observations [54]. They could determine that catalyst productivity is affected by an increment of terminal olefins in the reaction mixture. Most olefin metathesis catalysts are unstable as methylidene complexes, which are formed in the presence of terminal olefins and, more importantly, in the presence of ethylene [55]. Further conclusions drawn from this study were that **C3** is active at least in the order of hours for this chemistry (far longer than originally presumed) and that the catalyst efficiency might be maximized with the development of processes for either selective product removal or for catalyst removal/recycling at low conversions.

The bulk ethenolysis of methyl oleate was performed by Forman et al. using a phoban-indenylidene catalyst [38]. As for the SM of methyl oleate, this readily available catalyst demonstrated to be a suitable alternative to **C3**, affording the desired products in 64% conversion with a catalyst load of 0.005 mol%, at 50°C and 10 bar of ethylene. Using the same conditions, **C3** led to a conversion of 43%.

The modification of ruthenium-based alkylidene complexes as a way to improve their performance in the ethenolysis of internal olefins continued to be investigated. Grubbs et al. reported the evaluation of a series of ruthenium olefin metathesis catalysts bearing cyclic(alkyl)-(amino) carbenes (CAACs, more electron donating than their traditional NHC counterparts) for the bulk ethenolysis of methyl oleate [56]. The tested reaction conditions were 40°C and ~10 bar of ethylene. At a loading of 0.01 mol%, all investigated catalysts exhibited good selectivities (73–94%) toward the CM products and achieved TONs between 4,200 and 5,600. The effect of lowering the catalyst loading to 0.001 mol% was also investigated for the best performing catalyst of the series, obtaining a conversion of 43%, a selectivity of 83%, and TON of 35,000. Furthermore, Schrodi et al. performed a detailed comparison of the performance of 15 ruthenium carbene-based catalysts in



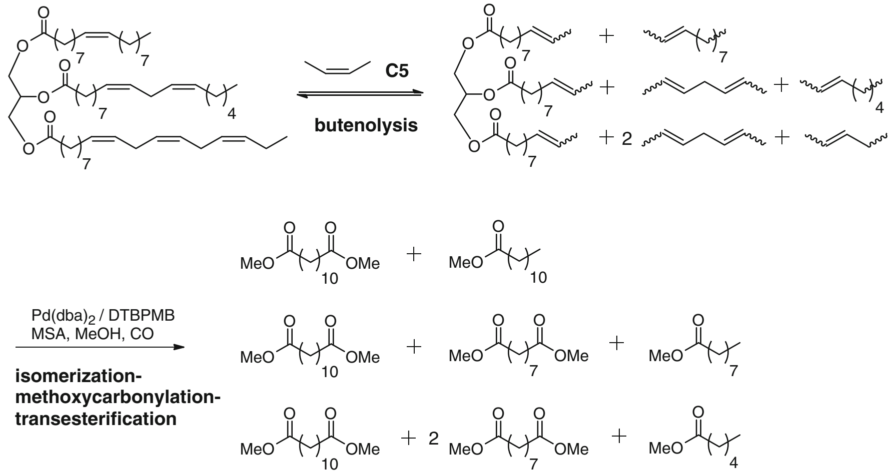
Scheme 4 Products of the ethenolysis of methyl oleate and highly efficient catalysts for this transformation developed by Grubbs [56], and Schrock and Hoveyda [59]

the ethenolysis of methyl oleate [57]. From the results of the study, they could conclude that several NHC-based ruthenium catalysts lead to better selectivities and activities than the well-known **C4** and **C5**. Also concerning the development of modified ruthenium metathesis catalysts, Grubbs and coworkers reported on the activity of ten different *N*-aryl, *N*-alkyl NHC ruthenium complexes in the ethenolysis of methyl oleate [58]. These catalysts gave selectivities as high as 95% and conversions up to 89% (Scheme 4). Moreover, the study revealed that ruthenium complexes bearing sterically hindered NHC substituents afforded greater selectivity and stability and exhibited longer catalyst lifetime. However, they pointed out the low TONs reached (below 6,000) as a limitation to be overcome in future investigations.

In an application-focused work, Grubbs and coworkers developed a microreactor for the continuous-flow ethenolysis of methyl oleate [59]. This microchemical system was based on a gas–liquid dual-phase design, allowing for the efficient diffusion of ethylene in methyl oleate through an increased contact area. The results at 4.1 bar of ethylene were comparable to the results of batch reactions at 10.3 bar of ethylene. A sterically hindered CAAC-based ruthenium catalyst gave 80% conversion and 87% selectivity with only 0.005 mol% catalyst (Scheme 4). The recovery and reuse of the catalyst after the ethenolysis of fatty esters are highly desirable if commercial applications are the objective. In this aspect, Dixneuf et al. studied the ethenolysis of methyl oleate at room-temperature ionic liquids (RTILs) [60]. After the reaction, a simple extraction of the products and unreacted substrate with heptane left the ionic liquid phase (containing the catalyst) for further catalytic runs. Thus, using Hoveyda–Grubbs first-generation catalyst in [bdmim][NTf_2] at 20°C and 10 bar of ethylene, a conversion of 83% was achieved with 100% of selectivity. Although this reaction media required a higher catalyst loading (6.5 mol%) than in toluene (2.5 mol%), the Hoveyda–Grubbs first-generation catalyst used could be reused for three consecutive runs without loss of activity.

In 2009, Schrock, Hoveyda, and coworkers published the impressively efficient ethenolysis of methyl oleate in the presence of an imido alkylidene monoaryloxide monopyrrolide (MAP) complex of molybdenum [61]. A selectivity of 99% in combination with 95% conversion was obtained with 0.02 mol% catalyst loading, at room temperature and 10.1 bar of ethylene (Scheme 4). On the other hand, the related tungstacyclobutane catalyst gave lower yields, either at room temperature or at 50°C; however, selectivity was still 99%. The explanation for the different yields was based on the rate of ethylene release from the unsubstituted metallacyclobutanes, which is supposed to be the rate-determining step and is faster for molybdacyclobutanes. Another suggested explanation was a possible inhibition of the catalyst by a stronger binding of the ester carbonyl to tungsten compared to molybdenum.

In order to increase the sustainability of chemical processes, environmentally friendly solvents such as supercritical fluids (SCFs) are widely investigated. Han and coworkers studied the ethenolysis of ethyl oleate in SC CO_2 in relation with the phase behavior of the reaction mixture [62]. They carried out the ethenolysis reaction at 35°C in the absence of CO_2 and in the presence of CO_2 at three different pressures (50, 82, and 120 bar). The reaction in the absence of CO_2 reached equilibrium in 1 h at 80% conversion. The reaction rate in the presence of 50 bar of CO_2 was higher than without CO_2 and, at 82 bar, again increased with respect to 50 bar. However, when the pressure was increased to 120 bar, the reaction rate decreased. This effect was explained according to the variations on the phase behavior with the pressure: an increase in the CO_2 pressure carried an increase of solubility of reactants, products, and CO_2, which produced a decrease of the viscosity of the reaction mixture. This positive effect was enhanced at 82 bar and was accompanied by an increase of selective solubility of the products in the vapor phase that further increased both reaction rate and conversion. The decrease of efficiency at 120 bar was related to an increase of the solubility of the reactants in the CO_2 phase.



Scheme 5 Synthesis of α- and α,ω-diesters from plant oils via butenolysis and subsequent isomerization–methoxycarbonylation–transesterification sequence [63]

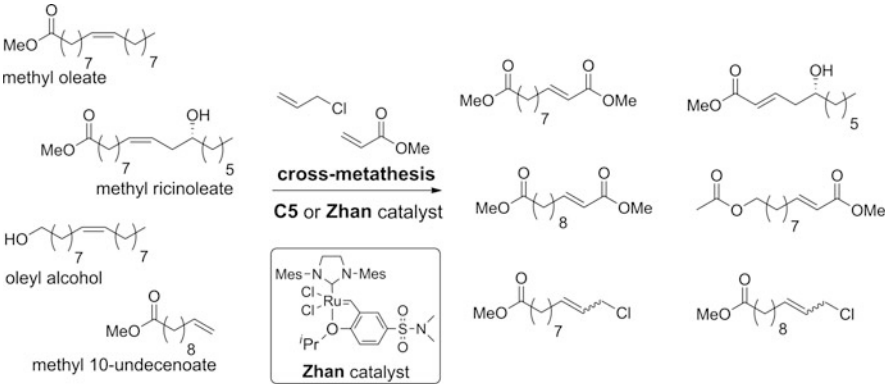
While the ethenolysis of fatty acids and esters yields α-olefins and ω-unsaturated acids and esters, the use of higher olefins or functionalized olefins as CM partners gives access to a wide spectrum of platform chemicals. The wide availability of ethylene makes ethenolysis particularly attractive; however, the associated problems regarding loss of catalyst activity already explained have motivated the search for alternative low molecular weight olefins. In this way, 2-butene (butenolysis) has been used to avoid the mentioned problems. Patel et al. reported the butenolysis of different natural oils in the presence of **C5** [63]. TONs between 23,000 and 93,000 could be obtained using triolein, together with a selectivity of 96% and a conversion of 95%. However, they found that in order to obtain optimum results, high purity 2-butene had to be used. The reason for this was the presence of some amount of butadiene in commercial grade *cis* + *trans*-2-butene, which was acting as a catalyst poison. The butenolysis of methyl oleate also gave good results using the same catalyst [64]. The purity of methyl oleate was again the key to obtain good TONs. While commercial methyl oleate gave a TON of 1,800 at a catalyst loading of 0.02 mol% and −5°C, triply distilled methyl oleate gave a TON of 470,000 with a catalyst loading of 0.0002 mol%. Furthermore, conversion of natural oils into terminal oxygenates was carried out by the same group of researchers following a butenolysis–isomerization–methoxycarbonylation–transesterification protocol (Scheme 5) [65]. This method, although leading to similar products than ozonolysis, offers the possibility of fractionating the intermediate products to facilitate selective methoxycarbonylation and production of target esters. Moreover, conversions over 98% with selectivities over 95% were described.

The olefin metathesis of biodiesel (mixture of fatty acid methyl esters) in the presence of 1-hexene was used by Meier et al. as a way to improve the distillation curve of this class of fuel [66]. Normally, biodiesel has a constant boiling point (i.e., ~330°C for rapeseed methyl ester) in contrast with the steady distillation curve displayed by diesel fuel, which contains a mixture of compounds boiling between 160 and 400°C. Thus, ten ruthenium-based catalysts were screened at 40 and 50°C for the bulk CM of biodiesel with 1-hexene at catalyst loading between 0.02 and 0.1 mol%. The conversions reached were found between 90% and 98% with five of the catalysts tested when 0.1 mol% was used. However, when the catalyst loading was lowered to 0.05 mol%, only **C4**, **C5**, and $\mathbf{M5_1}$ from the company Umicore ([1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro[2-(1-methylacetoxy)phenyl]-methyleneruthenium(II)) still maintained the conversion over 95%. Further lowering of the catalyst loading significantly reduced the conversions (below 80%). Despite the similar conversions obtained with these three catalysts, $\mathbf{M5_1}$ displayed the highest TONs (>2,000) even with 0.03 mol% loading. Thus, 0.05 mol% $\mathbf{M5_1}$ at 50°C was selected as the best option. Using the optimized reaction conditions, the boiling curve of biodiesel was successfully modified by varying the amount of 1-hexene. Moreover, the catalyst was efficiently removed (>99%) by treatment of the reaction mixture with hydrogen peroxide.

The CM of fatty acids and derived compounds also has been used for the production of fine chemicals that are difficult to obtain by other synthetic approaches. Some examples include the synthesis of a plant growth stimulant, an insect pheromone precursor, the sex pheromone of the peach twig borer moth, and others [28]. Furthermore, the conjugation of fatty acid derivatives, sugars, and amino acids via CM was shown by Vernall and Abell [41]. **C4** with a catalyst loading of 20 mol% was used to perform the CM of either *N*-Boc-L-lysine or *N*-Boc-L-cysteine bearing a 10-undecenoic chain with methyl 10-undecenoate or a sugar olefin.

Brändli and Ward prepared a library of internal olefins through self-metathesis and CM of a variety of derivatives of oleic acid, namely, methyl oleate, oleic acid, oleyl amine (which did not react), oleyl alcohol, and other olefins [42]. These reactions were performed using 1 mol% of **C3** and led to statistical product mixtures that were analyzed by GC–MS and NMR.

The production of α,ω-diesters from fatty esters can be realized via their SM as already explained, but it can also be performed by CM with methyl acrylate. The bulk CM of several unsaturated fatty acid methyl esters containing double bonds in different positions with methyl acrylate was studied by Rybak and Meier (Scheme 6) [43]. **C4** and **C5** displayed very good activities with high conversions and CM selectivities. Among them, **C5** showed the best performance for both methyl oleate (97% conversion, 92% selectivity, with 0.2 mol%) and methyl 10-undecenoate (99% conversion, 99% selectivity, with 0.1 mol%). The same conditions were successfully applied to methyl erucate and methyl petroselinate. The reaction conditions were further optimized, also considering the effect of 1,4-benzoquinone as additive for the reduction of double-bond isomerization [39]. The CM of methyl 10-undecenoate and methyl acrylate worked with full conversions and high selectivity if five- to tenfold excess of methyl acrylate is used. Furthermore, using a 1:1 ratio between both reactants led, after optimization of the reaction

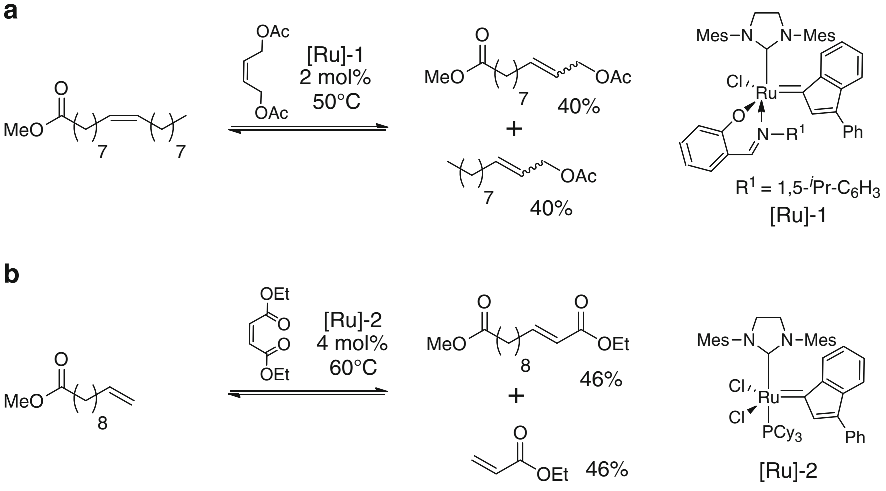


Scheme 6 Synthesis of renewable α,ω-difunctional compounds via CM of fatty acid-derived compounds with methyl acrylate or allyl chloride [41–44]

conditions, to conversions over 97% and selectivities over 90%. The CM of methyl ricinoleate with methyl acrylate, on the other hand, results in two difunctional compounds (Scheme 6). A design-of-experiment (DoE) approach was used by Ho and Meier to obtain, using the information of a small number of experiments, a predictive model for the optimization of this reaction [44]. **C5** and the Zhan catalyst were used and different reaction parameters considered. Furthermore, Yinghuai et al. performed the CM of methyl oleate with methyl acrylate using **C5** immobilized on the surface of magnetic nanoparticles [45]. An isolated yield of 60% was obtained with a catalyst loading of 0.2 mol% (Ru) at 45°C, and the catalyst was recovered by means of an external magnet and reused without loss of activity.

Oleyl alcohol is another interesting CM partner for methyl acrylate since it can directly provide a ω-hydroxyester suitable for polyester synthesis. Rybak and Meier studied this bulk reaction in the presence of **C5** and its environmental impact in relation with different factors [67]. Quantitative comparisons of the different synthetic approaches were made with EATOS (environmental assessment tool for organic syntheses), revealing that the protection of the alcohol group previous to the CM reaction, a necessary step to reduce the catalyst loading, was also beneficial in terms of environmental impact (e.g., showed a lower overall E-factor). Thus, 1 mol% of catalyst led to 99.5% conversion and 96.2% selectivity to CM products using a fivefold excess of methyl acrylate (Scheme 6). Moreover, the recycling of unreacted starting materials was shown to have a large influence on the overall environmental impact.

Apart from methyl acrylate, allyl chloride was used to synthesize α,ω-difunctional monomers via bulk CM of methyl oleate and methyl 10-undecenoate (Scheme 6) [68]. While **C4** failed with yields below 20%, **C5** and the Zhan catalyst were able to catalyze the reaction with good results. Using **C5**, the best yield (90%) for the CM of methyl oleate was obtained at 50°C and 1 mol% catalyst using a fourfold excess of allyl chloride. The Zhan catalyst performed similarly, but gave

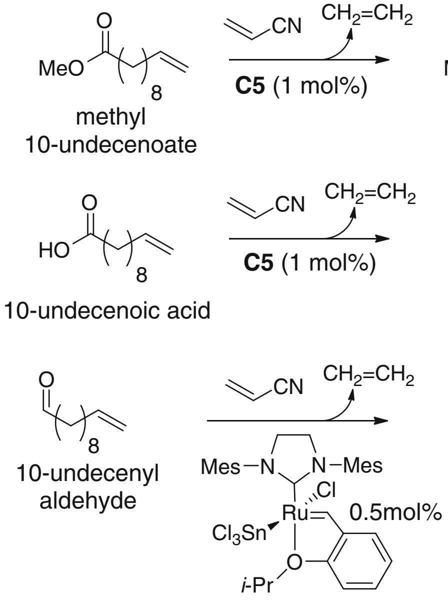


Scheme 7 Cross metathesis with symmetric olefins, (**a**) methyl oleate with *cis*-2-butene-1,4-diyl diacetate [67], and (**b**) 10-undecenoate with diethyl maleate [68]

better results at low catalyst loadings (72% yield with 0.1 mol% and two equivalents of allyl chloride). Concerning methyl 10-undecenoate, the Zhan catalyst also gave better results at low catalyst loadings; however, the best results were obtained with 1% of **C5** (79% yield of CM products).

The use of symmetric olefins as CM partners of fatty esters is advantageous since the olefin released can also react to give the desired product. Examples of this approach have been described by Behr et al. The CM of methyl oleate with *cis*-2-butene-1,4-diyl diacetate was studied in the presence of eight different ruthenium-based catalysts with a catalyst loading of 1 mol%, in toluene at 50°C, and using a fivefold excess of the symmetric olefin [69]. The highest conversions (34–90%) were reached with the NHC ruthenium catalysts with a maximum yield of CM products of 60%. Further optimization using the best performing catalyst revealed an increase of both conversion and CM selectivity with the increase of catalyst loading, obtaining the best results with 2 mol% (96% conversion, 64% CM yield). When the amount of symmetric olefin was increased, the conversion did not vary (around 96%); however, the CM yield was increased to ca. 80% by using a tenfold excess (Scheme 7a). The reaction time was shown to affect the CM yield (higher at long reaction times), but not the conversion of methyl oleate. Moreover, a decrease of the reaction temperature from 50 to 30°C decreased both conversion and yield. In addition to this, the reaction was performed with the unprotected olefins, i.e., oleic acid and *cis*-2-butene-1,4-diol. In this case, catalyst loadings up to 4 mol% had to be used in order to reach 75% conversion and 55% yield of CM products.

A similar study described the CM of methyl 10-undecenoate with diethyl maleate [70]. The performance of six ruthenium-based catalysts was tested for this reaction, and as in the previous study, all reaction parameters were screened for

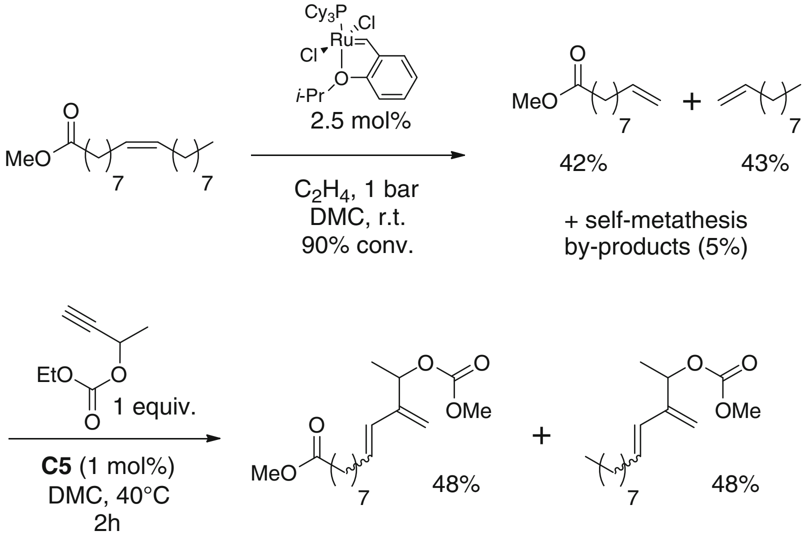


Scheme 8 CM of 10-undecenoic acid-derived platform chemicals with acrylonitrile [70]

optimization. A second-generation ruthenium indenylidene catalyst was found to give the best results (99% conversion, 93% yield of CM) with a catalyst loading of 4 mol%, at 60°C, and using eight equivalents of diethyl maleate (Scheme 7b).

Another alternative for the production of α,ω-difunctional compounds from oleochemicals is the CM with acrylonitrile or fumaronitrile. These reactions give access to nitrile esters or acids with potential application in the synthesis of polyamides [71]. The CM of methyl oleate, methyl 10-undecenoate, and 10-undecenoic acid with acrylonitrile and fumaronitrile was studied by Dixneuf et al. [72]. These reactions were performed in the presence of **C4** and **C5**, observing the best activity for the latter in all cases (Scheme 8). Thus, the CM of methyl 10-undecenoate and acrylonitrile gave a conversion of 95% at a catalyst loading of 1 mol%, and the CM of 10-undecenoic acid gave, under the same conditions (1 mol%, toluene), 90% conversion at 100°C. Moreover, the CM of methyl oleate and acrylonitrile (two or four equivalents) proceeded with full conversion and very high selectivity with 5 mol% catalyst. Moreover, the same results could be obtained when fumaronitrile was used instead. The same reactions were performed following a tandem ruthenium-catalyzed CM and hydrogenation, which provided precursors of amino acid monomers for the production of polyamides from renewable resources.

10-Undecylenyl aldehyde, which can be derived from castor oil, has also been used as CM partner of acrolein and acrylonitrile [73]. **C5** (1 mol%) led to 94% isolated yield of the α,ω-nitrile-aldehyde by reaction with acrylonitrile in toluene at 80°C. A twofold excess of acrylonitrile was necessary to prevent the production of



Scheme 9 Ethenolysis-enyne CM sequence for the synthesis of fatty acid-derived conjugated dienes [48]

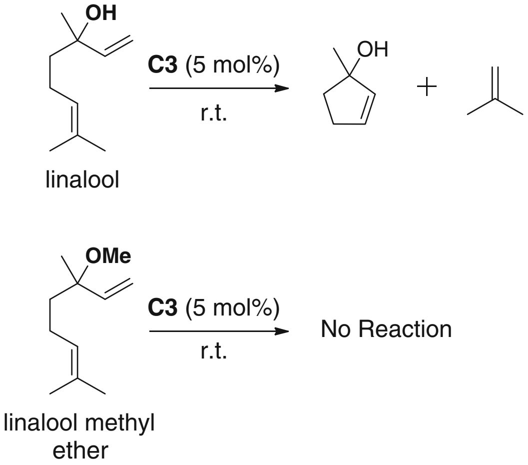
the aldehyde SM product. This reaction was later on successfully accomplished using a modified **C5** [48]. The insertion of $SnCl_2$ into only one Ru–Cl bond provided a new catalyst suitable for CM of long-chain olefins, which gave a conversion of 91% at a catalyst loading of 0.5 mol% (Scheme 8). Furthermore, this complex catalyzed the CM of an internal olefin-containing diester to 99% conversion at a catalyst loading of 1 mol%. Further work was devoted to the optimization of these reactions by a protocol based on the slow addition of catalyst, which provided TONs up to 1,900 (92% yield) for cross metatheses of methyl 10-undecenoate, dimethyl octadec-9-en-1,18-dioate, and methyl ricinoleate with acrylonitrile [74]. Moreover, when these conditions were applied to the CM with methyl acrylate, TONs up to 7,600 were obtained. It was also shown that the second-generation Hoveyda type catalysts are the most efficient for these transformations.

The ene-yne CM of fatty acid-derived terminal alkenes with several alkyne derivatives was shown by Bruneau et al. [75]. These reactions, which led to renewable conjugated dienes, were performed in a one-pot two-step procedure. In the first step, the ethenolysis of methyl oleate was performed in the presence of the first-generation Hoveyda–Grubbs catalyst (2.5 mol%) using dimethyl carbonate as solvent at room temperature. After completion of the ethenolysis (90% conversion), **C4** (1 mol%) and the corresponding alkyne (0.5 equivalents with respect to olefins) were added and the reaction was run at 40°C for 2 h (Scheme 9). The desired dienes were thus obtained in high yields close to the maximum theoretical value (50%). Moreover, in order to maximize the formation of functional dienes, the same reaction sequence was applied to the diester obtained by SM of methyl oleate. In this way, the yield of functional dienes was increased up to 90% depending on the alkyne used. These investigations were extended by studying the effect of a slow alkyne addition to the reaction mixture [76]. This method allowed the use of stoichiometric amounts of olefin and alkyne with similar yields of enyne CM products (up to 94% for methyl oleate), thus increasing the sustainability of these transformations. Moreover, this protocol was applied for the ethenolysis/enyne CM of methyl ricinoleate in the presence of **C5**, although a moderate yield of 42% was obtained.

2.2 Terpenes

Up to date, olefin metathesis has not often been applied to terpenes. There are a number of reports available that use different terpenes as building blocks for the synthesis of molecules of higher complexity; however, in most cases, olefin metathesis was applied to already modified structures. Some reports in this context include the synthesis of (*R*)-(−)-muscone from (*R*)-(+)-citronellal [77], the synthesis of α,ω-unsaturated lactones linked to a variety of terpenoid skeletons via RCM [78], the SM of modified artemisinin (a sesquiterpene lactone) to form dimers with potent anticancer activities [79], an approach to germacratrienes (sesquiterpenoids) from the monoterpene chiron (−)-carvone including an RCM step [80], the synthesis of (−)-platencin from (−)-perillaldehyde also using RCM [81], or the syntheses of stereoisomers of the female-produced sex pheromone of a moth, *Lyclene dharma dharma*, taking enantiomers of citronellal as starting materials [82]. Concerning the direct application of olefin metathesis to terpenes and terpenoids, Nugent et al. reported the RCM of (*R*)- and (*S*)-citronellene in the presence of the oxo-tungsten complex *trans*-$WOCl_2(OAr)_2$, which was easily prepared by reaction of $WOCl_4$ with two equivalents of 2,6-dibromophenol [83]. The products, (*R*)- or (*S*)-3-methylcyclopentenes, were obtained with 68% and 70% yield and 97% enantiomeric excesses. Later on, the RCM of linalool in the presence of **C3** was studied by Hoye and Zhao [84]. Linalool underwent fast RCM with a catalyst loading of 5 mol %, which was unexpected for a structure containing a fully substituted allylic position. Moreover, this ring closing involves a trisubstituted alkene, making the result even more surprising. In order to understand this phenomenon, the reactivity of linalool was compared to that of citronellene, which has the same structure lacking the hydroxyl group. Although the steric hindrance is lower in citronellene, linalool reacted faster. Further reactivity comparisons were performed with the alcohol group protected as ether (Scheme 10), leading to the conclusion that allylic hydroxyl groups accelerate the rate of carbene-exchange reaction between the adjacent vinyl group and the external ruthenium alkylidenes, thus overcoming the steric deactivation. The same high efficiency in the RCM of linalool was reported by Fogg and coworkers using three different ruthenium pseudohalide catalysts [85]. They could reach up to 100% conversion in 15 min using 0.5 mol% of catalyst. Linalool was also used by Nolan and coworkers as substrate for RCM [86]. Three second-generation ruthenium-based complexes bearing *N*-naphthylsubstituted

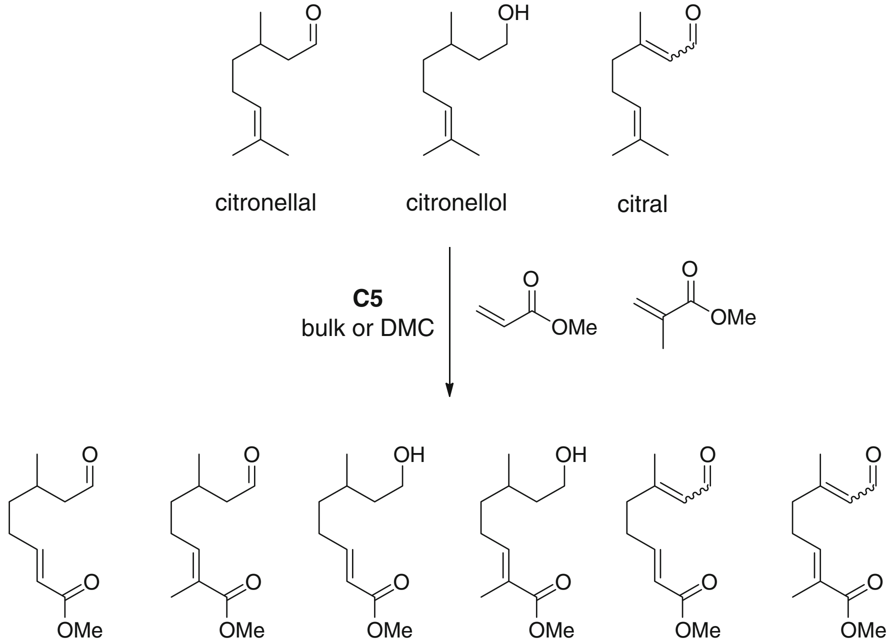
Scheme 10 Positive effect of the allylic alcohol of linalool in its RCM reaction [82]



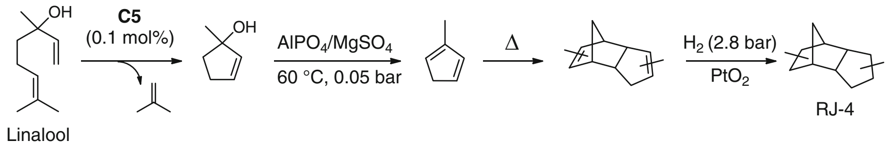
NHC ligands in catalyst loadings of 0.1 and 0.5 mol% were used at room temperature. Using these conditions, isolated yields between 88% and 94% were obtained.

The direct transformation of terpenes and terpenoids via CM has been treated in only a few reports. Bruneau et al. reported the access to difunctional terpenoids from citronellal, citronellol, and citral through CM with either methyl acrylate or methyl methacrylate [87]. Four commercially available ruthenium-based metathesis catalysts were tested, and dimethyl carbonate was used as an environmentally friendly solvent (Scheme 11). The CM of citronellal with methyl acrylate reached 100% conversion and 70% isolated yield in the presence of 0.5 mol% of **C5**, while the CM with methyl methacrylate needed a higher catalyst loading (2%) to prevent undesired methyl methacrylate polymerization and reach a conversion of 90%. The same catalyst led to the best results when citronellol was used, both in the CM with methyl acrylate (90% conversion, 53% isolated yield with 0.5 mol% of catalyst) and methyl methacrylate (100% conversion, 70% isolated yield with 2 mol% catalyst). Citral, containing an additional internal double bond, and thus a more challenging substrate, was also subjected to CM. In the reaction with methyl acrylate, **C5** displayed the best activity, giving quantitative conversion with 2 mol% loading. However, the occurrence of secondary reactions gave an isolated yield of only 42%. When methyl methacrylate was used, 4 mol% of catalyst was necessary to avoid gelification and reach 100% conversion (40% isolated yield).

Taking linalool as starting material, Harvey et al. described an interesting approach to renewable high-density fuels [88]. The characteristics of this class of fuels, which are used in jets, missiles, and other special applications, include high density and flash point, and low freezing point. The method used was based on the RCM of linalool followed by dehydration of the alcohol under mild conditions, and low-temperature thermal dimerization to methylcyclopentadiene dimer, which can readily be converted into a high-density fuel (Scheme 12). In the first step (RCM), **C5** (0.1 mol%) was used and a yield exceeding 95% in a 30 g-scale reaction was obtained. The RCM product was then dehydrated in the presence of $AlPO_4/MgSO_4$



Scheme 11 Products obtained in the CM of citronellal, citronellol, and citral with methyl acrylate or methyl methacrylate [85]



Scheme 12 RCM of linalool as a first step of the synthesis of the high-density fuel RJ-4 [86]

at 60°C and 0.05 bar. A mixture of methyl cyclopentadienes was thus obtained that underwent room-temperature dimerization. The subsequent hydrogenation of the mixture of dimers led to RJ-4, a commercial high-density liquid fuel.

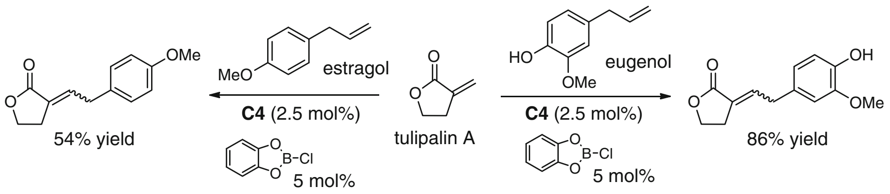
CM reactions with terpenoids containing two double bonds such as citronellene are hampered by low yields because of RCM competition among other side reactions. Mauduit et al. performed the CM of several terpenoids with *n*-butyl acrylate and crotonaldehyde using Hoveyda–Grubbs type catalysts containing an aminocarbonyl function [89]. Yields below 43% were obtained in all cases with 1 mol% catalyst. In contrast to these results, the hydrated masked form of citronellene, i.e., dihydromyrcenol, gave 71% yield of the CM product. It was thus proposed that in order to avoid selectivity problems in the CM of terpenoids containing two double bonds, masked derivatives can be used followed by a simple elimination step to recover the olefin functionality.

Terpenoid derivatives containing a carbonyl group were transformed in a two-step procedure by Bruneau et al. into propargylic ene-ynes [90]. The cyclization of these products via ene-yne metathesis was performed in the presence of a catalytic system generated in situ from $[RuCl_2(p\text{-cymene})]_2$, 1,3-bis(mesityl)imidazolinium chloride and Cs_2CO_3, affording a new class of terpenoids with a 0.5 mol% catalyst loading (Ru) in toluene at 80°C. This work was continued with the synthesis of silylated 1,7-enynes from natural carbonyl-containing terpenoids [91]. The enyne CM cyclization of these derivatives was performed with the same in situ-prepared catalyst using loadings between 1.25 and 2.50 mol% (Ru).

2.3 Other Natural Products

Also produced by plants, phenylpropanoids possess double bonds suitable for olefin metathesis. The CM of eugenol, as a representative example, has been studied with different olefins. Taber and Frankowski studied its CM with *cis*-1,4-butenediol in the presence of 2 mol% of **C4** [92]. They could observe similar results (86% yield) when using the catalyst dispersed in paraffin wax (as a way of catalyst preservation) and when using the pure catalyst. Nolan and coworkers reported the CM of eugenol using three second-generation ruthenium-based complexes bearing *N*-naphthylsubstituted NHC ligands [84]. Using methyl acrylate at a catalyst loading of 1 mol% led to yields between 68% and 92%. Similar results were obtained using *cis*-1,4-butenediol as CM partner (yields between 78% and 86%), and in all cases, some dimeric material was observed due to SM. Both eugenol and estragol were used by Cossy and coworkers as olefinic partners of tulipalin A (α-methylene-γ-butyrolactone), a butyrolactone produced by tulips [93]. In this study, **C4** proved to be the most efficient. Moreover, the effect of several additives to suppress double-bond isomerization in the reaction with 4-methylpentene was tested. Among all of them, 2,6-dichloro-1,4-benzoquinone and chlorocatecholborane (5 mol%) completely avoided or highly reduced isomerization. However, chlorocatecholborane, although still allowing some isomerization, led to the highest isolated yield (87%). Therefore, this additive was tested in the CM of tulipalin A with 20 different olefinic partners (including eugenol and estragol, Scheme 13), obtaining moderate to high yields of the target products in all cases at a catalyst loading of 2.5 mol%.

A similar study was performed by Howell et al., in which isomerization during the CM of tulipalin A with 1-acetoxy-9-decene was investigated [94]. In the absence of any additive, and using **C5**, only the isomerization product was obtained; however, addition of 10 mol% of 2,6-dichlorobenzoquinone completely avoided isomerization, leading to the product in 98% yield. The results were similar in the CM with other olefins reaching yields between 43% and 93%. The polyunsaturated structure of β-carotene was subjected to ethenolysis by Morzycki et al. with the aim of producing vitamin A derivatives [95]. Among different ruthenium-based complexes tested with 20 mol% catalyst loading at room temperature, only



Scheme 13 CM of tulipalin A with estragol and eugenol [89]

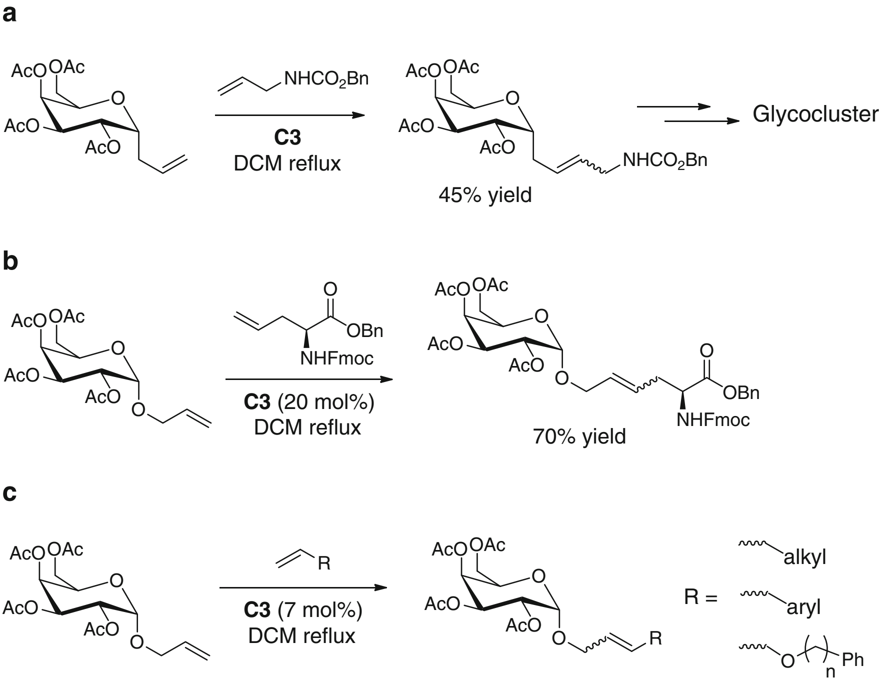
C5 promoted the ethenolysis reaction, leading to formation of three main products. Furthermore, the CM of β-carotene with acrylonitrile and 4-bromobut-1-ene was successfully performed in the presence of the same catalyst, observing the same regioselectivity as in the ethenolysis reaction.

2.4 Non-Olefinic Renewable Compounds

There is a wide range of renewable platform chemicals which, although not naturally containing double bonds, can be readily modified in order to apply olefin metathesis. Among them, carbohydrates, proteins, and amino acids are targets of a large variety of studies involving chemical modifications due to their implication in biological processes. For this reason, olefin metathesis is preferred over other routes since it generally offers a straightforward alternative to more complex synthetic pathways. Some representative examples will be discussed below.

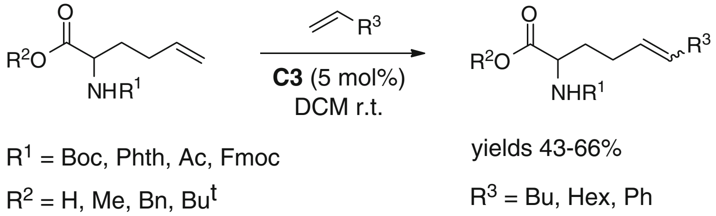
One of the main focuses of carbohydrate chemistry is the design and synthesis of artificial neoglycoconjugates (carbohydrate-containing constructs that contain structural and functional elements of naturally occurring glycoconjugates). In order to understand and manipulate biological processes involving carbohydrates, neoglycoconjugates are advantageous over natural compounds since they can be tailor-made to display similar or improved biological activity. Neoglycoconjugates are classified in a number of groups according to their structure, and among them, olefin metathesis has been applied for the synthesis of glycopolymers, glycoclusters, glycophanes, neoglycopeptides, neoglycolipids, and others [96]. Glycopolymers will be addressed in the second part of this chapter, dedicated to the synthesis of polymers via olefin metathesis.

The synthesis of glycoclusters mediated by olefin metathesis was first reported by Roy and coworkers, sharing the CM of a variety of C-glycosides with protected allylamine as initial step (Scheme 14a) [97]. The same group reported on the synthesis of a glycocluster through a series of self-metathesis and CM reactions starting from allyl 2,3,4,6-diisopropylidene-α-mannoside [98]. The work reported on the preparation of glycophanes (hybrids of carbohydrates and cyclophanes) is relatively recent; however, many examples have arisen since this class of structures could find application in bioorganic, medicinal, and supramolecular chemistry [99]. Neoglycopeptides are the products of CM between alkene-containing



Scheme 14 CM of carbohydrates as key step for the synthesis of (**a**) glycoclusters [92], (**b**) neoglycopeptides [96], and (**c**) neoglycolipids [97]

carbohydrates and amino acids. The resulting glycosyl amino acids are interesting structures that can easily be built into peptide-like glycoclusters or glycopeptides, and in the case of C-glycosylalkenes, metabolically stable glycopeptide analogues can be generated [100]. A representative example of the utility of CM in the synthesis of such biologically active hybrids can be found in a work by Danishefsky's group [101]. The CM of allyl glycosides with Fmoc-L-allylglycine benzyl ester afforded complex glycosyl amino acids in the presence of 20 mol% of **C3** (yields up to 70% when using five equivalents of L-allylglycine, Scheme 14b). This method was also applied to the breast and prostate cancer antigen Globo-H, obtaining a hexasaccharide glycosyl amino acid that had been previously incorporated in a polyvalent antitumor vaccine. The synthesis of neoglycolipids is also of interest. The lipid moiety of glycolipids is critical for cell-membrane and cell-wall assemblies and for various cellular signaling processes. For this reason, studies have been carried out on the effect of introducing different lipid segments. Wong and coworkers reported the synthesis of a library of glycolipids by using CM as the key step to diversify the lipid moiety of anomerically pure α- or β-glycosides (Scheme 14c) [102]. Some of these glycolipids displayed optimal properties as lipid linkers for the noncovalent attachment of glycolipids to microtiter plates, and two of them showed interesting results in a CD1d-based immunoassay.



Scheme 15 CM of protected amino acids with aryl and alkyl olefins [102]

Turning to proteins, the chemical modification of their structure is a powerful method for the study and modulation of their macromolecular function [103]. However, in order to use olefin metathesis as the synthetic tool, several issues must be considered. First, an alkene functionality must be introduced to the protein. Then, generally, the reaction should preferentially work efficiently in water at or below 37°C, and a metathesis catalyst that tolerates the complex structure of the protein must be found. Moreover, the secondary and tertiary structure of the protein must not hinder the access to the site of modification. The Davis group pioneered this field by first examining the CM of simple amino acid models with allyl alcohol in aqueous media [104]. **C5** (6 mol%) was used. Among all substrates tested, allyl sulfides showed the best qualities as CM partners for the studied conditions; it was proposed that the sulfur atom might coordinate to the metal center favoring the approach of the reacting sites. In the next step, a single cysteine mutant of the serine protease subtilisin *Bacillus lentus* (SBL) was modified to *S*-allyl cysteine and subsequently subjected to CM with different olefins. This work was extended by an in-depth study on allylic chalcogen effects using different substrates [105]. In this regard, allyl selenides were found to be highly reactive CM substrates. Moreover, guiding principles in metathesis partner selection were introduced.

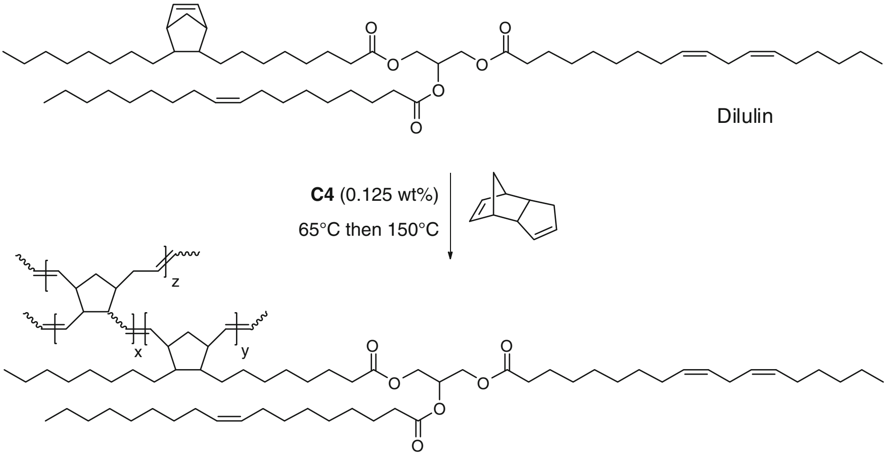
Amino acids have been frequently used as substrates in olefin metathesis reactions. In an early example from 1995, Miller and Grubbs prepared a variety of conformationally constrained amino acids and peptides employing RCM reactions [106]. This strategy was effective both with protected and free amide NH groups and for the synthesis of covalently stabilized β-turn mimetics. All reactions were catalyzed by a Grubbs first-generation catalyst in 5 or 20 mol% (for the more challenging synthesis of the β-turn) loading, which led to yields between 50% and 90%. In relation to CM, Gibson et al. reported the first examples [107]. **C4** was shown to catalyze the CM of variety of protected forms of the amino acid homoallylglycine with aryl- and alkyl-substituted alkenes in acceptable yields between 43% and 66% (Scheme 15). An interesting approach to olefin containing α-amino acids was described by Rutjes et al. [108]. α-Amino acids bearing a ω-unsaturated side chain were synthesized through an enzymatic route and then used as CM partners of various olefins in the presence of 5 mol% of **C4** (isolated yields from 40% to 75%).

3 Synthesis of Polymers

Olefin metathesis is also a highly versatile technique for the synthesis of polymers from renewable resources. In this respect, especially ADMET polymerization and ROMP have been used to prepare macromolecules starting from fatty acid precursors due to their inherent double-bond functionality. Nevertheless, also other feedstock and methods have been applied, as will be reviewed within this section.

3.1 Plant Oils and Fatty Acids

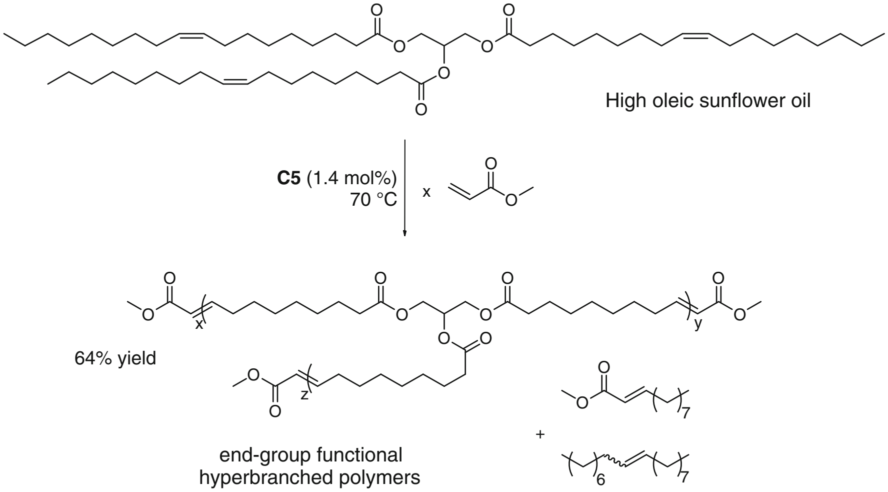
Plant oils and derived compounds have been extensively used directly or as precursors of monomers for polymer synthesis via olefin metathesis. Concerning ROMP, dicyclopentadiene (DCPD) was copolymerized with a commercially available vegetable oil derivative possessing an unsaturated bicyclic moiety (Dilulin, Scheme 16) using **C4** to prepare promising glass fiber-reinforced composites by Larock and coworkers [109]. Similarly, Dilulin was polymerized with **C3** in the presence of a bicyclic norbornene-based cross-linking agent to yield resins with good thermal stability [110]. When Dilulin was copolymerized with DCPD via ROMP, T_gs ranging from −29 to 36°C were obtained, depending on the ratio of reactants [111]. The thermal stability, measured as T_{max} by TGA, on the other hand was almost independent of the composition and found at about 460°C. Moreover, cyclooctene was copolymerized with a castor oil derivative containing norbornene functional groups, which was obtained by esterification of the OH groups of the ricinoleic acid moieties with bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride [112]. A **C4** concentration of 0.5 wt% was found optimal to obtain full cross-linking; the resulting materials showed T_gs close to or somewhat below 0°C and thermal stability up to 200°C (T_{max} ~460°C). Moreover, the ROMP of different ratios of norbornenyl-functionalized castor oil and norbornenyl-functionalized castor oil alcohol using **C4** resulted in rubbery to rigid renewable plastics [113]. Glass transition temperatures of up to 65°C and storage moduli of up to 830 MPa could be reached via this approach. Additionally, the ROMP of norbornenyl-functionalized fatty alcohols from soybean oil and a variety of other monomers was studied by the same group [114]. The resulting materials were thoroughly studied by Soxhlet extraction, DMA, TGA, and tensile tests, revealing properties that were comparable to petroleum-based plastics such as HDPE and poly(norbornene). A different approach was taken by Meier et al. by functionalizing saturated fatty acids of various carbon chain length with norbornene moieties and subsequently polymerizing these monomers via living ROMP with **C6** [115]. Low polydispersities (1.05–1.21) in combination with the possibility to target the degree of polymerization, linear first-order kinetics, and possible chain extension revealed a living polymerization behavior of these plant oil-derived monomers. Thermally



Scheme 16 Copolymerization of Dilulin with DCPD via ROMP for the synthesis of glass fiber-reinforced composites [104]

quite stable materials (5% weight loss at ~325°C) with T_gs ranging from 102°C (C_6 fatty acid) to −32°C (C_{18} fatty acid) were thus obtained.

The ADMET polymerization of plant oils is especially attractive since it can be performed directly on these natural compounds. Due to the high double-bond functionality of plant oils, this reaction leads to cross-linked products unless chain stoppers are used. Furthermore, the properties of these materials vary in a wide range depending on the fatty acid distribution of the plant oils used. The first reports on the SM of plant oils are based on the use of the catalytic system WCl_6–$(CH_3)_4Sn$, already mentioned in the previous section, which presents a poor stability toward moisture and oxygen [116–118]. Later on, the advent of ruthenium-based catalysts provided access to the efficient polymerization of plant oils. Larock and coworkers polymerized a series of natural plant oils in the presence of **C3** [119]. Alcohol-insoluble materials were produced in yields between 40% and 60% using optimized conditions. This work was completed with a study on the ADMET polymerization products obtained using triolein as substrate [120]. The same catalyst was used at a 0.1 mol% loading, leading to trimer, tetramer, pentamer, as well as monocyclic oligomers, although high molecular weight monocyclic oligomers were predominant. Using these reaction conditions, soybean oil was successfully transformed into a variety of materials, from sticky oils to rubbers. With a different objective, Meier and coworkers showed that the acyclic triene metathesis (ATMET) polymerization of glyceryl 10-undecenoate (a model triglyceride) in the presence of methyl acrylate as chain stopper yields hyperbranched polymers [121]. The addition of methyl acrylate not only avoided cross-linking but also provided a simple way to modulate the molecular weight of the polymer by varying the amount added. ^{1}H-NMR analysis allowed to estimate the degree of polymerization of these macromolecules and revealed the presence of



Scheme 17 ATMET polymerization of high-oleic sunflower oil in the presence of methyl acrylate as chain stopper [115]

macrocycles. This method enabled the one-pot synthesis of end group-functionalized hyperbranched polymers. The same strategy was applied to high oleic sunflower oil as a natural substrate with similar results (Scheme 17) [122]. **C5** was used at a 1.4 mol% loading, and subsequent analysis of the ATMET products with ESI-MS showed the presence of highly branched and functionalized structures. *Plukenetia conophora* oil, a seed oil containing about 70% of linolenic acid, was also polymerized via ATMET to produce highly branched macromolecules [123]. Metathesis catalysts **C4**, **C5**, and **M3$_1$** ([1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(3-phenyl-1H-inden-1-ylidene)(pyridyl)ruthenium(II)) and **M5$_1$** from the company Umicore were tested in 1.5 mol% loading. In all cases, non-cross-linked branched polymers were obtained with oil conversions between 80% and 88%. GPC analysis of these polymers showed PDIs between 2.30 and 3.94 and M_w between 12 and 29 kDa. The polymer obtained with **C5** at 90°C was analyzed by dynamic light scattering in DMAc, which revealed the presence of particles with a mean diameter of 6 nm, and its rheological properties were evaluated. Furthermore, the branched polymers synthesized presented T_gs around −60°C, melting transitions close to 0°C, and onset degradation temperatures (5% weight loss) above 290°C.

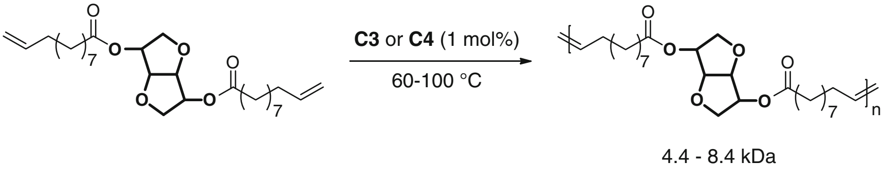
In another example, branched polyols were synthesized by Meier, Ronda et al. [124] via ATMET polymerization of glyceryl triundec-10-enoate in the presence of 10-undecenol. Also here, 10-undecenol was used as chain stopper, allowing control over the molecular weight and providing hydroxyl functionalities as end groups. The Zhan metathesis catalyst (0.4 mol%) was added in portions at different reaction times to avoid cross-linking. These polyols were reacted with MDI, producing a set of cross-linked semicrystalline polyurethanes (PUs), some of which had good shape memory properties. A different study from Küsefoğlu et al. also dealt with the

ATMET of a triglyceride-based multifunctional monomer [125]. The ring opening of epoxidized soybean oil with 4-vinyl benzene sulfonic acid provided monomers suitable for metathesis polymerization. The bulk reaction of this monomer in the presence of **C5** afforded a thermosetting material with a T_g of -1.6°C.

ADMET polymerization, when applied to α,ω-dienes, yields strictly linear polymers. Warwel et al. reported the synthesis of unsaturated polyesters via ADMET of fatty acid-based α,ω-dienes in 2001 [126]. The monomers were prepared by transesterification of methyl esters of 9-decenoic acid, 13-tetradecenoic acid, and 10-undecenoic acid with diols of varying alkyl chain lengths. Several homogeneous and heterogeneous catalytic systems were tested, and among the homogeneous ones, the fluorinated molybdenum Schrock complex provided the best results (up to 41,100 g/mol). 10-Undecenoic acid has been used by Meier et al. as building block for the synthesis of a variety of ADMET monomers. For instance, high molecular weight unsaturated polyesters were synthesized with an α,ω-diene prepared by esterification of 10-undecenoic acid with 10-undecenol [127]. With a catalyst loading as low as 0.5 mol% of **C4**, a molecular weight (M_n) of 22 kDa was obtained. Methyl 10-undecenoate was used as chain stopper to control the molecular weight of these polyesters and to generate telechelics. Moreover, ABA triblock copolymers were prepared by using oligomeric poly(ethylene glycol) as chain stopper. In this case, however, **C5** (1 mol%) was used. Later on, the homopolymer was also used by Mecking et al. in the preparation of aqueous polyester dispersions [128]. The dispersions were obtained by emulsification via ultrasonication of a toluene solution of the unsaturated homopolymer in an aqueous surfactant solution. This was followed by exhaustive hydrogenation with Wilkinson's catalyst at 60°C and 80 bar H_2 to produce a dispersion with an average particle size of 35 nm (dynamic light scattering and transmission electron microscopy analyses). The same α,ω-diene was used as comonomer in the ADMET polymerization of a phosphorus-based monomer, also containing two 10-undecenoic acid moieties [129]. The thermal- and flame-retardant properties of the copolymers obtained could be varied by changing the ratio of both monomers. Furthermore, in a related work, unsaturated polyesters containing pendant hydroxyl groups were prepared via ADMET and subsequently acrylated [130]. Further radical cross-linking afforded flame-retardant thermosets.

The 10-undecenoic acid motif has also been attached to isosorbide in the preparation of a fatty acid-/carbohydrate-based monomer [131]. ADMET polymerization in the presence of **C3** and **C4** produced fully renewable unsaturated polyesters (Scheme 18). Most importantly, the transesterification of these polyesters with MeOH, and subsequent analysis by GC–MS of the products, allowed for the quantification of double-bond isomerization during ADMET in a very simple manner. This strategy was then extended to fatty acid-based ADMET polyesters synthesized in the presence of indenylidene metathesis catalysts [132]. With these studies, the knowledge on the olefin isomerization in ADMET reactions was widened, and it is now possible to almost completely suppress this undesired side reaction.

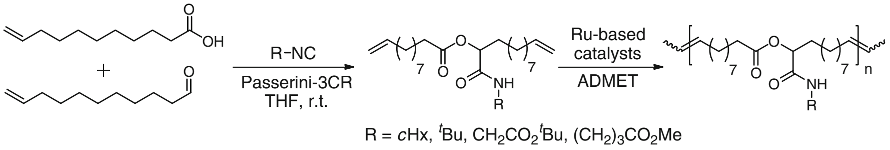
Monomers derived from 10-undecenoic acid with amide functional groups have been polymerized via ADMET as well [133]. However, the low tolerance of



Scheme 18 ADMET polymerization of a fatty acid-/carbohydrate-based α,ω-diene [126]

metathesis catalysts toward amides was reflected on the low molecular weights obtained with both **C4** and **C5** (M_n up to 6 kDa with catalyst loadings 5–10 mol%). However, in this case, the high melting points of the produced polyamides influenced the results since stirring was difficult at the studied temperatures. Another study aimed the preparation of biodegradable polymers via ADMET [134]. Monomers containing either ester or anhydride connectivity were polymerized in the presence of Zhan catalyst (1 mol%, 80ºC). In this way, polyesters and polyanhydrides were obtained from monomers constructed from 10-undecenoic acid. Moreover, random copolymers were synthesized. The hydrolytic stability of these polymers was tested in both acidic (H_2SO_4 in THF) and enzymatic (Novozyme 435 in THF) conditions at 37°C. Degradation took place in all cases being faster for the polyanhydride in both media, and in general, the enzymatic degradation was slower. Interestingly, the random copolymer displayed intermediate degradation behavior, indicating the possibility of tuning the degradation properties of this class of polymers by simply changing the monomer ratio.

The self-aldol condensation of 10-undecenal, also derived from castor oil, produces an α,ω-diene containing an α,β-unsaturated aldehyde. This monomer was polymerized in the presence of several metathesis catalysts at 80°C [135]. Although the aldehyde functionality is usually not well tolerated by these catalysts, four of the tested catalysts provided good results, especially **C5**, which gave polymers with M_n around 11 kDa. The reduction of the aldehyde groups in the polymers obtained provided a poly(allyl alcohol) structure, of interest regarding potential post-polymerization modifications. A novel approach for the synthesis of castor oil-based ADMET monomers, also involving 10-undecenal, consisted on the Passerini three-component reaction (Passerini-3CR) of 10-undecenoic acid and 10-undecenal with different isonitriles (Scheme 19) [136]. This strategy produced α,ω-dienes (isolated yields 59–83%) with amide groups as pendant chains and were subsequently polymerized via ADMET in the presence of several ruthenium-based complexes. Among the tested metathesis catalysts, **C3** failed and **C5** showed the best activity at 80°C and a loading of 1 mol%. In this way, molecular weights between 11.5 and 21.6 kDa (M_n) were obtained. Moreover, one of the produced polymers was modified following a grafting-onto strategy performing additional Passerini reactions in the side chains. These results were complemented by comparing the Passerini-ADMET sequence with a CM-poly-Passerini approach. Thus, both an α,ω-diacid and an α,ω-dialdehyde were prepared by CM of castor



Scheme 19 Synthesis of 10-undecenoic acid-based α,ω-dienes via Passerini-3CR and polymerization via ADMET [131]

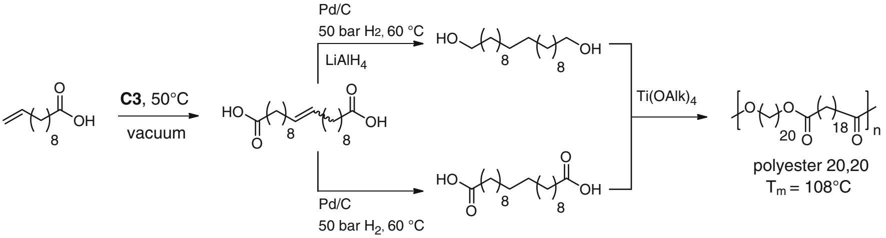
oil-derived chemicals and reacted with isonitriles in a poly-Passerini-3CR. Interestingly, higher molecular weight polymers were obtained with the second approach (up to 56.5 kDa).

Among other utilities, ADMET is a unique tool to produce polyethylene-like materials with controlled structure [137]. In this regard, fully renewable polyethylene was synthesized via ADMET of undeca-1,10-diene, a monomer derived from castor oil, followed by palladium-catalyzed hydrogenation [138]. About 1 mol% of **C3** and **C4** were used with similar results (M_n up to 11 kDa). Furthermore, a similar castor oil-based monomer containing an ether group was prepared. The polymerization of this monomer gave the best results in the presence of Grubbs second generation (M_n 16 kDa), and the hydrogenation of the resulting polymer yielded a polyethylene-like material.

Ferulic acid, a phenolic acid that can be found in rapeseed cake, has been used in the synthesis of monomers for ADMET homo- and copolymerization with fatty acid-based α,ω-dienes [139]. Homopolymerizations were performed in the presence of several ruthenium-based olefin metathesis catalysts (1 mol% and 80°C), although only **C5**, the Zhan catalyst, and catalyst **M5$_1$** of the company Umicore were able to produce oligomers with T_gs around 7°C. The comonomers were prepared by epoxidation of methyl oleate and erucate followed by simultaneous ring opening and transesterification with allyl alcohol. Best results for the copolymerizations were obtained with the erucic acid-derived monomer, reaching a crystalline polymer (T_m −24.9°C) with molecular weight over 13 kDa.

Cross-linked PUs with shape memory properties were prepared by Galià, Meier et al. using linear polyols synthesized by ADMET [140]. In this work, ADMET of a 10-undecenoic acid-derived α,ω-diene containing a hydroxyl group was performed in the presence of 0.1 mol% of **C4**. 10-Undecenol was used as chain stopper, and the mixture of oligomers and diols (from 10-undecenol SM) obtained was cross-linked with MDI. The PUs obtained displayed outstanding values of strain fixity and recovery.

The complementary approach to ADMET for the synthesis of plant oil-based polyesters is the SM of fatty acids, esters, or alcohols, followed by classic polycondensation of the generated α,ω-difunctional compounds. In 2001, Warwel and coworkers showed the self-metathesis of different ω-unsaturated fatty esters and their subsequent polycondensation in the presence of diols and $Ti(OBu)_4$ or Ca

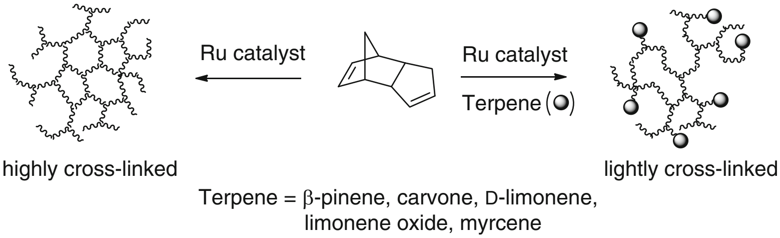


Scheme 20 Synthesis of polyester 20,20 by polycondensation of α,ω-diester and α,ω-diols prepared via SM of 10-undecenoic acid [123]

(ac)$_2$/Sb$_2$O$_3$ as catalysts [121]. For the SM reactions, **C2** and **C3** were used. High molecular weight polyesters up to 110 kDa could be obtained following this strategy. Mecking and coworkers have also used a similar approach [123]. The SM of 10-undecenoic acid in the presence of **C3** and subsequent exhaustive hydrogenation yielded pure 1,20-eicosanedioic acid. No isomerization of the double bond was observed in the SM step. Reduction of the diacid gave eicosane-1,20-diol, and polycondensation of both products catalyzed by titanium alkoxides produced a polyester of 10 kDa (Scheme 20).

As already noted by Verkuijlen and Boelhouwer in 1974 [29], the SM of highly unsaturated fatty esters produces, among other compounds, considerable amounts of 1,4-cyclohexadiene (1,4-CHD). This fact has been exploited by Mathers et al. for the production of 1,3-cyclohexadiene (1,3-CHD) via metathesis and isomerization reactions of plant oils [141]. For instance, 1,4-CHD was obtained by treatment of soybean oil with **C4** and was subsequently isomerized with RuHCl(CO)(PPh$_3$)$_3$. Then, the produced 1,3-CHD was polymerized with nickel(II)acetylacetonate/methaluminoxane. Interestingly, the polymerizations could be carried out in bulk and using hydrogenated D-limonene as renewable solvent. The polymers thus obtained presented T_m around 300°C.

ADMET is a step growth polymerization in which all double bonds present can react in secondary metathesis events. However, olefin metathesis can be performed in a very selective manner by correct choice of the olefinic partner, and thus, the ADMET of α,ω-dienes containing two different olefins (one of which has low homodimerization tendency) can lead to a "head-to-tail" ADMET polymerization. In this regard, terminal double bonds have been classified as Type I olefins (fast homodimerization) and acrylates as Type II (unlikely homodimerization), and it has been shown that CM reactions between Types I and II olefins take place with high CM selectivity [142]. This has been applied in the ADMET of a monomer derived from 10-undecenol containing an acrylate and a terminal double bond (undec-10-en-1-yl acrylate) [143]. Thus, the ADMET of undec-10-en-1-yl acrylate in the presence of 0.5 mol% of **C5** at 40°C provided a polymer with 97% of CM selectivity. The high selectivity of this reaction was used for the synthesis of block copolymers and star-shaped polymers using mono- and multifunctional acrylates as selective chain stoppers.



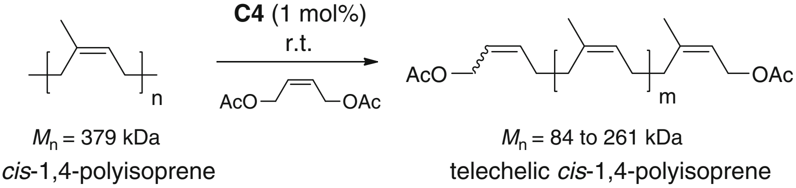
Scheme 21 Control of the cross-link density during the ROMP of DCPD with terpenes as chain stoppers [140]

3.2 Terpenes

Quite a few terpene-derived monomers were polymerized via ROMP thus far. For instance, Mathers et al. have used terpenes as renewable solvents and chain-transfer agents during the ROMP of various monomers. In their first paper, D-limonene was used during the polymerization of norbornene; 1,5-cyclooctadiene; cyclopentene; *trans*,*trans*,*trans*-1,5,9-cyclododecatriene; as well as cycloheptene [144]. Compared to ROMP in toluene, lower molecular weights were obtained due to chain transfer to solvent with the formation of telechelic polymers, as expected. More recently, the same concept has been used for the polymerization of DCPD [145]. First, the gelation time of a thermoset of DCPD with 40 wt% β-pinene was correlated to the investigated ruthenium catalysts in order to establish their activity for this reaction. After having established the basic reaction conditions, the authors could clearly demonstrate a correlation between the used monoterpene amount (β-pinene and carvone; 0–20 wt%) and the T_g (variation between 65°C and 150°C) as well as storage modulus (680–1,630 MPa), allowing them to tune the material properties of the obtained DCPD resins (Scheme 21). When a variety of monoterpenes was used in larger amounts as solvents, cross-linking was avoided during the polymerization of DCPD, thus resulting in hyperbranched polymers [146].

3.3 Natural Rubber and Other Olefinic Natural Compounds

Natural rubber, chemically speaking poly(*cis*-1,4-isoprene), is a natural polymer derived from *Hevea brasiliensis* and various other tropical plants like *Castilloa elastica* [147]. This natural polymer is mainly produced in Asia and the tropics in high, industrially relevant, amounts (e.g., 9.7 Mio mto in 2007). Apart from its usual use as an elastomeric material, some research was devoted onto the metathesis degradation (depolymerization) of natural rubber with ethylene in a CM fashion. It was believed that metathesis of natural rubber is impossible, until a pioneering



Scheme 22 Synthesis of telechelic acetoxy-terminated *cis*-1,4-polyisoprene by olefin metathesis depolymerization of natural rubber [144]

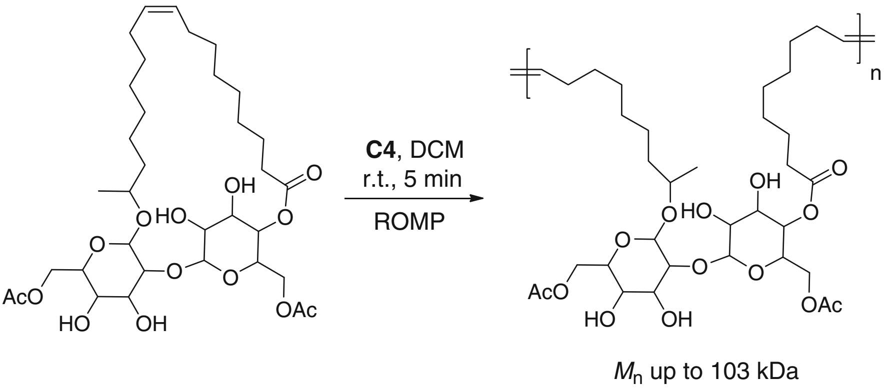
study by Alimuniar and Kohjiya et al. reported on the use of tungsten hexachloride and tetramethyl tin in chlorobenzene as the catalytic system for this reaction [148]. A sharp drop in molecular weight was observed upon SM of natural rubber due to inter- and intramolecular reactions (e.g., backbiting, cyclization, and others). Higher reaction temperatures resulted in lower molecular weights, and side reactions that decreased the amount of unsaturation, thus leading to better heat resistance, were observed. Later, degradation studies of *cis*-1,4-polyisoprene were performed using **C3** and **C4** to obtain telechelic acetoxy-terminated oligomers (Scheme 22) [149]. This was achieved by carrying out CM experiments of natural rubber with cis-1,4-diacetoxy-2-butene as a chain-transfer agent, which resulted in a rapid depolymerization to yield telechelics of various molecular weights via an ADMET mechanism. Undesired side reactions, as mentioned above, were not reported for these catalysts. Recently, Plenio et al. reported on the ethenolysis of natural rubber and squalene as a model substance using $(NHC)(NHC_{ewg})RuCl_2({=}CRR')$ and Hoveyda–Grubbs type initiators [150]. A screening of 12 catalysts under different reaction conditions revealed that indenylidene complexes generally performed better than benzylidene ones and that **C5** was similarly active to the best catalyst, but formed more secondary products. After these optimization studies, the results were transferred to natural rubber. In the latter case, the catalyst amount had to be increased from 0.01 to 0.1 mol% (per double bond) to achieve satisfactory results, and more side reactions were observed. Both results were related to possible impurities of the natural product.

Natural rubber oligomers with β-pinene terminal units have been synthesized by Gutiérrez and Tlenkopatchev via metathesis depolymerization [151]. The bulk degradation of natural rubber in the presence of β-pinene, as chain-transfer agent, and **C4** (0.1 mol% related to polymers with M_n between 490 and 1,700 kDa) produced monoterpene-terminated oligomers in yields between 80% and 90%. The results were further confirmed with model CM reactions using β-pinene and (*Z*)-3-methyl-2-pentene.

Taking eugenol and isoeugenol as starting materials, Luinstra et al. prepared a series of α,ω-dienes using the reactivity of the phenol group [152]. The ADMET polymerization of these monomers in the presence of **C4** afforded polyethers and polycarbonates in the range of 2,700–32,000 g/mol. The high viscosity of the reaction mixtures prevented the efficient removal of ethylene, limiting the molecular weights. Isomerization of the allylic double bond of eugenol to the more stable vinylic position was observed, being the reason for the formation of amorphous polymers.

3.4 Carbohydrates

Apart from the already discussed renewable polymers, also carbohydrate-containing monomers were polymerized via ROMP. For instance, β-cyclodextrin was functionalized with norbornene and subsequently polymerized using **C3** with the aim to use them as chiral selectors for capillary zone electrophoreses [153]. Unfortunately, not much information was provided about the polymerization behavior and/or the properties of the resulting polymers. Already in 1995, Grubbs et al. showed that well-defined (PDI 1.1–1.2) polymers can be prepared via ROMP of protected sugar-functionalized norbornenes via ROMP using ruthenium-based initiators under optimized experimental conditions [154]. Only 1 year later, Nomura and Schrock described the synthesis of “sugar-coated” polymers via ROMP using a molybdenum catalyst for the polymerization of norbornene-functionalized and acetal-protected sugars [155]. Narrow PDIs and high yields were observed; the “sugar-coated” polymers could then be fully deprotected using standard protocols to yield water-soluble materials. Generally, this is an interesting field of research and could result in so-called glycopolymers with various biological responses. However, since this kind of polymers only somewhat fits to the scope of this chapter, namely, renewable raw materials, only a few examples of glycopolymers prepared via ROMP will be shortly summarized. Nomura continued these investigations and published a series of manuscripts using similar monomers to result in various polymer architectures [156–161]. As one conclusion of these investigations concerning the metathesis performance of these monomers, the authors mentioned that molybdenum-based catalysts were better suited for these polymerizations than ruthenium-based systems [155]. Moreover, Kiessling et al. reported on a large variety of glycopolymers prepared via ROMP [162–164]. For instance, this group attached mannose units to a reactive polymer backbone prepared via ROMP, thus allowing the control of the number of recognition elements (via the DP of the polymer and the degree of functionalization) for subsequently performed lectin binding studies [165]. Saturated neoglycopolymers, prepared via tandem ROMP-hydrogenation of carbohydrate-functionalized norbornenes, were evaluated as collagen cross-linking agents for tissue engineering, revealing good performance [166]. Moreover, not only norbornene derivatives but also cyclooctene derivatives of protected sugars were used for ROMP [167]. A very interesting glycopolymer can be derived from a glycolipid monomer (sophorolipid biosurfactant in its natural lactonic form) [168]. This monomer (Scheme 23) can be obtained via fermentation in high yields, and its ROMP with the **C4** resulted in high molecular weight semicrystalline polymer ($M_n > 100$ kDa, $T_g = 48°C$, $T_m = 135°C$) in high yield. Such a polymer is indeed



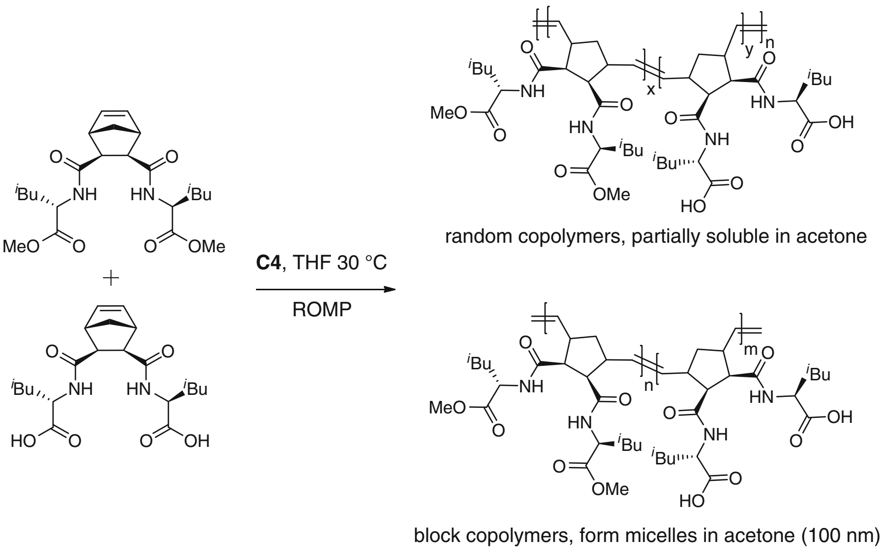
Scheme 23 ROMP of a sophorolipid [163]

much closer to the substitution of fossil materials and thus to be used as renewable polymer than the above-mentioned glycopolymers.

The ADMET polymerization of sugar-based monomers is much less explored than the ROMP approach, and only a few examples have been reported to date. Bui and Hudlicky prepared α,ω-dienes derived from a biocatalytically synthesized diene diol, from which chiral polymers (up to 20 kDa) with D-*chiro*-inositol units were prepared via ADMET in the presence of 1 mol% of **C4** [169]. Furthermore, several α,ω-dienes containing D-mannitol, D-ribose, D-isomannide, and D-isosorbide have been synthesized by Enholm and Mondal [170]. Also in this study, **C4** was used to catalyze the ADMET polymerizations at 1 mol% catalyst loading. As pointed out by the authors, the viscosity increased as the reactions progressed and vacuum had to be applied to efficiently remove the released ethylene. Unfortunately, the polymers obtained were not further analyzed. As already mentioned above, Fokou and Meier have also reported the ADMET polymerization of a fatty acid-/D-isosorbide-based α,ω-diene [126]. Furthermore, Krausz et al. have synthesized plastic films with good mechanical properties by cross-linking fatty esters of cellulose in the presence of **C3** [171–173].

3.5 Amino Acids

Synthetic protein-like polymers containing amino acids find pharmaceutical and biological applications and display self-assembly properties [174]. In this aspect, both ROMP and ADMET have been used as tools for the polymerization of amino acid-based monomers. Early ROMP examples date back to 1994 with the synthesis and ROMP of amino acid-derived homochiral norbornene monomers by Coles et al [175]. The molybdenum complex $[Mo(=CHCMe_2Ph)(=NC_6H_3Pr^i{}_2\text{-}2,6)(OBu^t)_2]$



Scheme 24 Synthesis of random and block copolymers via ROMP of amino acid-functionalized norbornenes [173]

was used, providing homochiral polymers with PDIs between 1.13 and 1.29. Many different approaches have been reported in the field since then. For instance, a direct application of ROMP was shown by Grubbs and coworkers, consisting of the synthesis of polymeric materials that were shown to be potent inhibitors of cell adhesion to the extracellular matrix protein fibronectin [176]. In fact, the synthesized peptide-containing homopolymer and copolymer (multidentate ligands) were 750% and 3,300% more active in a competitive inhibition experiment than the peptide itself. A different study on the bioactivity of amino acid-based ROMP polymers was reported by Sampson et al. [177]. They prepared norbornyl oligopeptides and polymerized them in the presence of **C3**. The resulting polymers, containing fertilin-β peptides as side chains, were tested as inhibitors of sperm–egg adhesion in a mouse in vitro fertilization assay, giving better results than the monomeric counterpart.

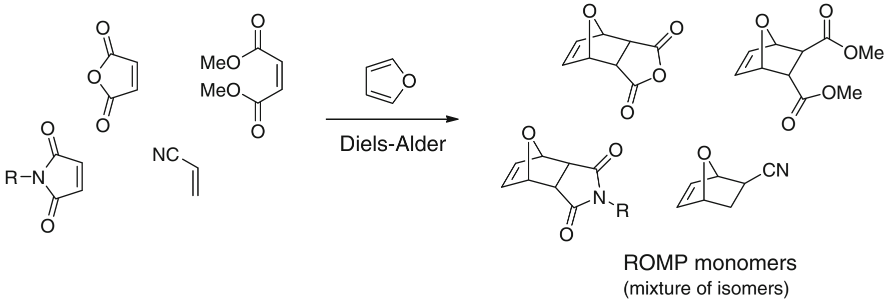
Amino acid-based norbornene random and block copolymers have been synthesized by Sanda, Masuda et al. [178]. The blocks were constructed with monomers containing either the ester or carboxyl amino acid forms, and **C4** was used. While the random copolymers were partially soluble in acetone, the block copolymers were soluble through formation of reverse micelles (Scheme 24). Moreover, the diameter of these aggregates was around 100 nm as measured by DLS and AFM. Amino acid-based ROMP monomers with a different cyclic core, i.e., cyclobutenecarbonyl glycine methyl esters, were polymerized by Sampson et al., leading to head-to-tail-ordered polymers without stereocenters [179]. **C6** was used and polydispersities between 1.2 and 1.6 were obtained.

A variety of ADMET monomers containing amino acids were synthesized by Wagener and coworkers. The polymerization of these α,ω-dienes in the presence of **C4** provided polymers with amino acid moieties either in the backbone or as side chains [180]. The monomers having the amino acids as pendant groups led to branched polymers with molecular weights between 21 and 31 kDa, and some of them presented melting temperatures as high as 135°C. Moreover, these polymers formed strong semicrystalline films. On the other hand, the polymerization of the linear monomers was clearly influenced by the methylene spacing between the carbonyl and the reacting double bond, most likely due to a negative neighboring group effect (NNGE) [181]. Following to this work, branched polyolefins containing amino acid and peptide branches were synthesized using 1 mol% of **C4**. It was shown that, when the functionality was attached through the N-terminus [182], the monomer polymerized more readily compared to the attachment at the C-terminus [183]. Regarding the thermal properties, the amino acid moieties were found to play a predominant role in their semicrystallinity. Investigations on the effect of introducing lysine as pendant group in polyethylene on each 21st carbon were also carried out using the same catalyst/loading [184]. As in previous reports, the crystallization behavior of the polymers obtained was mainly affected by the lysine pendant group, and not by the polymer backbone. Moreover, unexpectedly high crystallinity was observed, taking into account the atactic nature of the polymers.

Diketopiperazines (cyclic amino acid dimers) have been also employed in the synthesis of α,ω-dienes for ADMET polymerization. Masuda et al. prepared four L-glutamic acid diketopiperazine ω-alkenyl esters and polymerized them in the presence of **C4** and **C5** [185]. A strong NNGE prevented the polymerization when only one methylene separated the terminal olefin and the ester group. However, ADMET of the other monomers led to polymers with molecular weights between 4 and 15 kDa and melting points up to 159°C due to strong intermolecular hydrogen bonding between amide groups.

3.6 Others

Some other natural compounds have been transformed for their use in the synthesis of polymers via olefin metathesis processes. As mentioned in the introduction, furans, which are obtained from carbohydrates, are perfect precursors of monomers for ROMP via simple Diels–Alder cycloadditions (*n*) (Scheme 25) [26]. In this regard, the first example of the ROMP of 7-oxabicyclo[2.2.1]hept-5-ene derivatives was reported by Novak and Grubbs in 1988 using ruthenium- and osmium-based catalysts [186]. The number of examples of ROMP with monomers with this generic structure is vast, and it is out of the scope of this chapter to cover all of them. However, it is worth mentioning here the great potential of a renewable platform chemical like furan (and derived compounds), which gives access to such a variety of monomers.



Scheme 25 Synthesis of ROMP monomers via Diels–Alder cycloaddition of furan with different dienophiles [26]

4 Conclusion

This chapter provides an overview of the research performed to date in the field of olefin metathesis with renewable platform chemicals and derived compounds. The high amount and variety of examples presented, covering both the synthesis of chemicals and polymers, evidence the potential of renewables as olefin metathesis substrates. Plant oils and fatty acids have been preferred unsaturated substrates, but also terpenes and terpenoids, natural rubber, furans, and other plant-derived compounds have been used. Moreover, carbohydrates, amino acids, and peptides have been also employed after functionalization with olefins. In addition, this field of research is of major significance since the use of platform chemicals derived from depleting sources, such as petrol, is no longer a sustainable option for the production of useful monomers and polymers for our society. In this context, olefin metathesis has to overcome some practical issues such as the high price of the catalysts before being fully applied in the industry; however, the excellent performance of metathesis catalysts in industrially relevant applications such as ethenolysis, the synthesis of α,ω-difunctional monomers, or ROMP is a good reason to believe in the transfer of olefin metathesis from the labs to the industry in a relatively short term.

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Pd-Catalyzed Telomerization of 1,3-Dienes with Multifunctional Renewable Substrates: Versatile Routes for the Valorization of Biomass-Derived Platform Molecules

Pieter C. A. Bruijnincx, Robin Jastrzebski, Peter J. C. Hausoul, Robertus J. M. Klein Gebbink, and Bert M. Weckhuysen

Abstract The dimerization of 1,3-dienes (e.g. butadiene) with the addition of a protic nucleophile (e.g. methanol) yields 2,7-octadienyl ethers in the so-called telomerization reaction. This reaction is most efficiently catalyzed by homogeneous palladium complexes. The field has experienced a renaissance in recent years as many of the platform molecules that can be renewably obtained from biomass are well-suited to act as multifunctional nucleophiles in this reaction. In addition, the process adheres to many of the principles of green chemistry, given that the reaction is 100% atom efficient and produces little waste. The telomerization reaction thus provides a versatile route for the production of valuable bulk and specialty chemicals that are (at least partly) green and renewable. The use of various multifunctional substrates that can be obtained from biomass is covered in this review, as well as mechanistic aspects of the telomerization reaction.

Keywords Biomass • Butadiene • Oxygenates • Palladium • Telomerization

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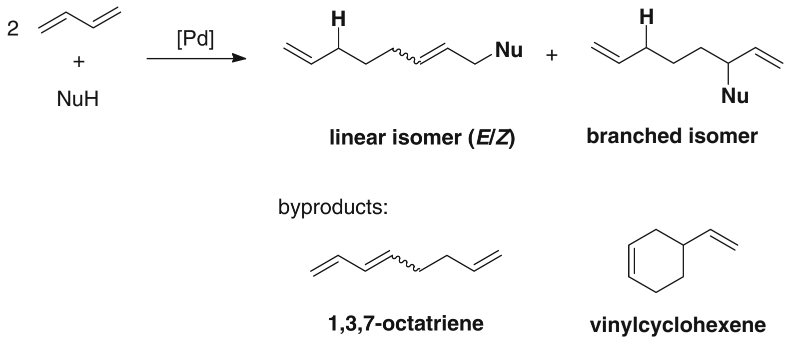
Contents

1 Introduction

The term telomerization is used to describe different processes in different fields of chemistry. The IUPAC compendium, for instance, lists telomerization as “the formation of an addition oligomer, . . ., by a chain reaction in which a chain transfer limits the length of the polymer (‘telomer’) produced”. In the context of homogeneous catalysis, telomerization instead refers to the dimerization or oligomerization of 1,3-dienes with addition of a nucleophile NuH. The nucleophile, or *telogen*, can be any nucleophilic compound as long as it has an “acidic” proton. The number of telogens used is therefore extensive and includes water, alcohols, phenols, amines, silanes, malonates, etc. The other component of the reaction is the 1,3-diene, the *taxogen* and most commonly 1,3-butadiene. The reaction can be catalyzed by various transition metals, including nickel, platinum and palladium. Homogeneous palladium complexes have emerged as the catalyst of choice for these telomerization reactions, however.

The palladium-catalyzed telomerization of 1,3-butadiene with the generic telogen NuH is given as a prototypical example in Scheme 1. Two products can be obtained, i.e. a linear or branched isomer, depending on the position of nucleophilic attack of the conjugate base of NuH. The linear isomer can be obtained with both *E* and *Z* geometry, with the *E* isomer typically being prevalent. Common side products include 1,3,7-octatriene, the linear dimerization product of 1,3-butadiene without addition of NuH, and to a lesser extent, vinylcyclohexane, the Diels–Alder product of 1,3-butadiene. The challenge in telomerization reactions is generally to limit the oligomerization of the 1,3-diene to dimerization, i.e. to avoid higher oligomers and to produce the linear isomer in high selectivity [1].

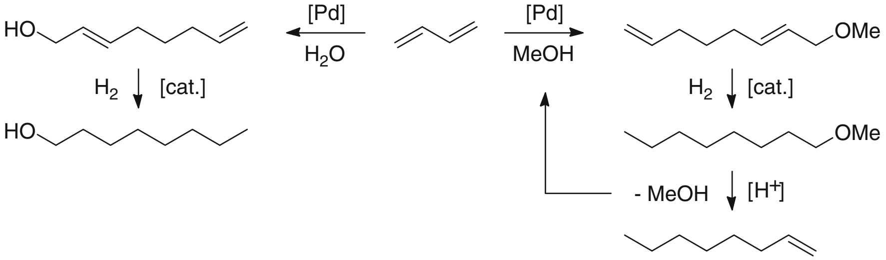


Scheme 1 Generalized reaction scheme for the Pd-catalyzed telomerization of 1,3-butadiene with nucleophile NuH

1.1 From Discovery to Commercialization

The telomerization reaction was discovered independently by both Smutny [2] and Takahashi et al. [3] in 1967, while working on the palladium-catalyzed dimerization of 1,3-butadiene. Smutny reported on the reaction between butadiene and phenol, which, in the presence of $PdCl_2$ as the catalyst and sodium phenoxide as a strong base, gave 96% conversion of phenol to 1-phenoxy-2,7-octadiene. The reaction proved remarkably robust, as it could be run over a broad temperature (0–150°C) and pressure range. It was also not sensitive to the addition of poisons and relatively free of by-products. Smutny already noted the importance of the presence of a strong base and that the reaction could also be run neat. In addition to various substituted phenols, other telogens such as carboxylic acids, alcohols and amines all could be successfully converted. The addition of triphenylphosphine to the crude reaction mixture after telomerization, at 0°C, yielded 1,3,7-octatriene after distillation under reduced pressure, already hinting at the fact that product formation is reversible for selected substrates. At around the same time, Takahashi and co-workers used a bis(triphenylphosphine)(maleic anhydride) palladium complex as catalyst in solvents such as acetone, benzene or tetrahydrofuran and first reported the formation of a dimerization product, identified as 1,3,7-octatriene, from butadiene. When done in alcohols or carboxylic acids, a mixture of the telomerization products and 1,3,7-octatriene was obtained. Methanol gave a 90% yield of mainly the linear product, whereas the more sterically hindered alcohol isopropanol mainly led to the production of 1,3,7-octatriene (72% yield based on butadiene) [3]. These first reports on the telomerization reaction thus not only demonstrated the broad scope of this rather versatile reaction, but also already included or pointed at many of the salient features of the process.

Since its discovery in the late 1960s, the telomerization process has matured and been commercialized. The Kuraray company first commercialized an application of the telomerization process in 1991 by producing the plasticizer 1-octanol on a scale of 5,000 ton/year via the dimerization of 1,3-butadiene with the addition of water to



Scheme 2 Two industrial processes involving a palladium-catalyzed telomerization step: the production of 1-octanol by Kuraray (*left*) and 1-octene by Dow Chemical (*right*)

yield 2,7-octadienol, which is in turn hydrogenated to 1-octanol (Scheme 2) [4, 5]. In 1992 [6], Dow Chemical patented the production of 1-octene, a comonomer for the production of linear low-density polyethylene, via a telomerization reaction. The process came on stream in 2008 in Tarragona and presumably consists of a palladium-catalyzed telomerization of 1,3-butadiene from the crude C4 fraction of the cracker with methanol to give 1-methoxy-2,7-octadiene. The product is then fully hydrogenated and subsequently cracked to 1-octene and methanol for recycle (Scheme 2). A similar process has also been patented by Oxeno Olefinchemie and was run on a pilot plant scale by Evonik Oxeno in Marl, Germany [7, 8]. Shell patented a telomerization process for 1-octene production that involves telomerization of butadiene with a carboxylic acid, e.g. acetic acid, followed by hydrogenation and pyrolysis of the resulting alkyl ester [9, 10]. If formic acid is used, 1,7-octadiene can be obtained after elimination of carbon dioxide from the formate ester, a process for which Evonik recently has shown interest [11]. Details of the routes to 1,7-octadiene and to 1-octene in particular can be found in a recent review by van Leeuwen [12].

In addition to the industrial developments listed above, much academic efforts have also been devoted over the years to (1) the expansion of the scope of the telomerization reaction, (2) the elucidation of the details of the reaction mechanism and (3) process modifications that allow more efficient production and separation of the desired products. The scope of substrates that can be used in this reaction has indeed been shown to be very broad. 1,3-Butadiene is most often used as the conjugated diene, since it is cheap, readily available and provides a linear octadienyl chain. The use of other dienes, such as isoprene [13–16], piperylene [17] and myrcene [18, 19], has also been described, but they have been far less commonly studied. Such substituted telogens come with an additional selectivity challenge as many more isomers can potentially be obtained, which is illustrated for isoprene in Fig. 1.

The variety of suitable nucleophiles is far greater; water, alcohols, phenols, amines and carboxylic acids are commonly used, but others including silanes or compounds with acidic C–H bonds such as malonates have been reported as well. The resulting products can, in some cases after further conversion, be used in many different applications, such as nonionic surfactants, emulsifiers, fragrances, flavouring agents, cosmetics and polymer components.

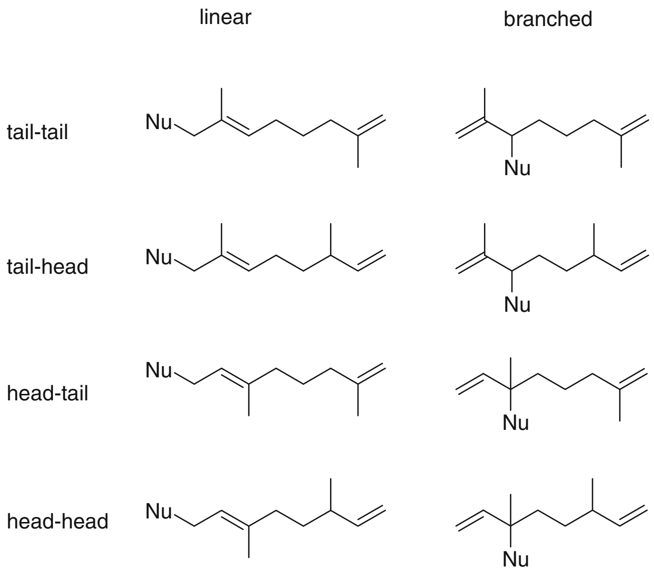


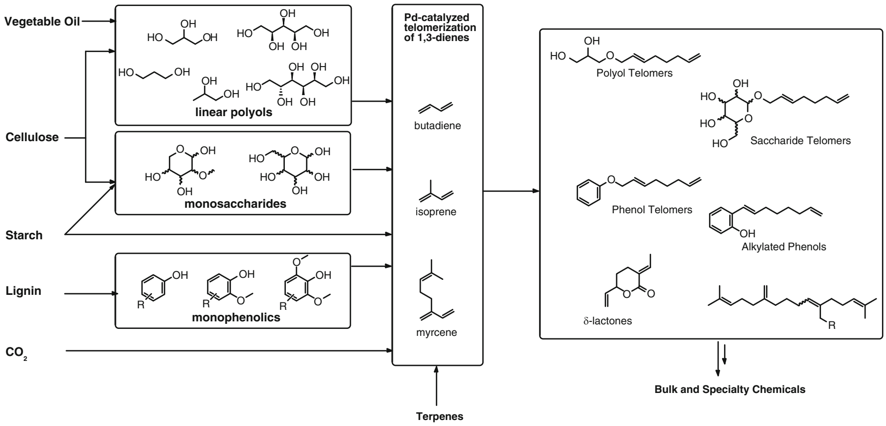
Fig. 1 Possible isomers that can be obtained in the telomerization of isoprene with NuH

1.2 Biomass-Derived Substrates: Specific Challenges and Opportunities

Concerns regarding global warming and the depletion of fossil fuel reserves combined with a projected increase in demand for energy and materials have put an emphasis on the realization of a transition from a fossil fuel-based society to one built on renewable resources. Such a transition should ultimately result in the development of fully fledged biorefinery operations which, similarly to the current petrochemical refineries, produce energy, liquid fuels and chemicals in a highly efficient and integrated manner. The production of bio-based chemicals in such a facility should not be overlooked as such high-value, lower-volume chemicals can generate the desired return on investment that is needed to make the biorefinery and its lower-value, high-volume biofuels economically feasible, as was recently advocated by Bozell and Petersen [20]. The pretreatment and further conversion of various bio-feedstocks, of which non-edible lignocellulosic biomass will feature prominently, into fuels, energy and chemicals will be built on a number so-called platform molecules, i.e. the compounds that will serve as the primary building blocks for further conversion to the various bulk and fine chemicals. This is again similar to the current petrochemical industry, where the multitude of chemicals used nowadays are essentially constructed from a very limited set of compounds that come out of the refinery (i.e. BTX, ethylene, propylene, 1,3-butadiene and methanol).

Bozell and Petersen recently compiled an updated yet dynamic list of top chemical opportunities from just the carbohydrate fraction that will be processed in the biorefinery. Many more targets can be envisaged, not just deriving from the polysaccharides but also from other sources such as lignin and the protein fraction of biomass, and it is not yet clear which compounds will be the eventual winners of the race. In any case, the development of new value chains and applications for these renewable chemicals and catalytic routes that go with it is essential. Although there is an overabundance of target molecules that can be obtained from biomass and a selection has to be made based on their market potential [20], they generally have in common that they are highly polar and highly oxygenated when compared to the current apolar and unfunctionalized hydrocarbons. While this general over-functionalization poses several difficulties for many of the envisaged valorization routes, these platform molecules are actually ideally suited to serve as multifunctional nucleophiles in telomerization reactions. Indeed, this has been widely recognized and has led to a current resurgence of the topic with much of the current effort aimed at the valorization of biomass-derived platform molecules. One has to point out here that the telomerization products are presently only partly based on renewable resources, with the most common taxogen butadiene being obtained from petrochemical steam cracking. In this light, the renewed interest in the old Lebedev process that converts (bio-)ethanol into 1,3-butadiene could eventually lead to fully renewable-based telomerization products that fit well in the integrated biorefinery concept. In addition to the use of renewable substrates, new chemical conversion processes should also preferably adhere to the concepts of green chemistry [21]. Telomerization reactions meet many of the important requirements in this respect, as they are in principle 100% atom efficient, are performed at low catalyst loadings of 2 ppm or less and are often run without the need of additional solvent or other additives.

A number of different opportunities for the valorization of biomass-derived platform molecules via telomerization are given in Scheme 3. Glycerol is, for instance, a by-product of the transesterification of triglycerides during the production of biodiesel. Sugars can be obtained from the hydrolysis of the polysaccharides hemicellulose, which make up the largest part of non-edible lignocellulosic biomass, or from starch. The polysaccharides themselves are also interesting nucleophiles for telomerization, and various reports on starch have been published and reviewed [22]. The sugars may be hydrogenated to the sugar alcohols or further converted to polyols by chemical or biotechnological means. The third major component of lignocellulosic biomass, lignin, is a highly aromatic polymer that, if suitable conversion processes can be developed, can serve as a renewable source of aromatics, phenolics in particular. Many efforts are currently devoted to the catalytic valorization of lignin [23]. The examples of the telomerization of phenolic substrates are therefore relevant and have also been included. Carbon dioxide can also be used as a renewable nucleophile for the production of δ-lactones, versatile building blocks that can be further converted to many other products, a topic which has recently been reviewed [24]. This telomerization reaction is currently one of the few processes that make direct use of this abundant renewable substrate into valuable chemicals. Finally, some 1,3-dienes can also be obtained from renewable



Scheme 3 Some examples of renewable oxygenates that can be used in the palladium-catalyzed telomerization of 1,3-dienes

resources. Terpenes, for instance, can be obtained from essential oils by simple distillation, providing access to more complex dienes, e.g. myrcene, which opens up possibilities for the synthesis of specialty chemicals.

Although many papers and patents concerning the telomerization process have appeared since its initial discovery, commercial application of the process is still limited to the two examples listed above. This reflects the potential of the reaction, but also the difficulties that are often encountered, for instance, with regard to achieving the required chemoselectivity and regioselectivity, i.e. discrimination between the two regio-isomers (or multiple isomers in case of dienes other than 1,3-butadiene). Challenges are often substrate dependent, but in all cases, they are usually largely influenced by experimental parameters such as the catalyst composition (e.g. P/Pd ratio). The nucleophile itself also influences the regiochemical outcome of the reaction, as phenols and acetic acid give more of the branched isomer than simple alcohols such as methanol do, for instance. Additional selectivity issues are encountered with multifunctional nucleophiles, as many isomeric products can be obtained. With regard to process efficiency, additional challenges lie in the recovery and reuse of the catalyst. All these aspects will be discussed below.

The focus of this review will be on those recent and older contributions to the telomerization field that primarily deal with the palladium-catalyzed telomerization with multifunctional oxygenates. First, a short glossary of commonly used ligands and catalysts is given, followed by a description of the mechanistic intricacies of the process and, finally, the different classes of multifunctional, renewable telogens that are treated in detail. This review complements two other excellent overviews of the telomerization reaction, each with its own primary focus. Behr and co-workers published an extensive review article summarizing the research on telomerization done in the period 1984–2008 with a particular focus on process developments [25].

Pinel and co-workers, on the other hand, recently reviewed the use of (poly) saccharides in the telomerization reaction as well as the physicochemical properties of the obtained products [22].

2 Typical Catalysts and Ligands Used in Telomerization Reactions

The ligands and catalysts that are typically used in the telomerization reaction will be shortly discussed in this section, and some recent developments will be highlighted. More details on the individual systems can be found in the sections below. A variety of ligands and catalysts have been explored with the purpose of increasing catalyst stability, activity and in particular selectivity. Initially, all efforts were focused on the use of phosphines and their water-soluble derivatives. The general practice of homogeneous catalysis of tuning catalytic activity and selectivity by optimizing the phosphine ligand design by electronic and steric modulation, e.g. by varying the nature and size of the substituents on the aryl rings, was followed, and progress is still being made in this respect. Beller et al. later reported on a second class of ligands that yield highly active, often superior, catalyst systems: the *N*-heterocyclic carbenes. Generally speaking, most of the efforts aimed at optimizing the ligand and/or catalyst have been focused on the two commercial examples of the telomerization reaction, i.e. those using water or methanol as the telogen. Some prominent ligands are depicted in Fig. 2.

Commonly used metal salts and palladium precursors include $Pd(OAc)_2$, Pd $(acac)_2$ (acac = acetylacetonato) and $Pd_2(dba)_3$ or $Pd(dba)_2$ (dba = dibenzylideneacetone). If a Pd(II) salt is used as pre-catalyst, reduction by base or by excess phosphine ligand is required. The exact nature of the reducing agent is somewhat contended, but it is often assumed that the phosphine takes up this role, for which evidence has been reported [26]. A typical catalytic system consists of a palladium source and an aryl- or alkylphosphine (typically PPh_3), in at least 2 eq., as ligand. The addition of bases, typically amines and alkoxides, is often found to be beneficial for activity, which is also reflected in the patent literature [27–29]. The bases are thought to facilitate in the attack of the nucleophile in the rate-determining step and, in the case of the amines, in the reduction of Pd(II) to Pd(0).

An extensive comparison of a large number of alkyl and aryl phosphines, including a number of chelating bis-phosphine ligands, was performed by Benvenuti et al. on the telomerization of 1,3-butadiene with methanol [30]. Bis-phosphines proved to be considerably less active than the monophosphines. Two additional correlations were found: use of phosphines with a larger Tolman cone angle results in a decrease in selectivity towards the telomer products and an increase in formation of 1,3-butadiene dimers, whereas increasingly basic phosphines give an overall increase in activity. This sensitivity of octatriene formation for the steric bulk of the catalyst, or the nucleophile, has been noted more often (vide infra, Sect. 3).

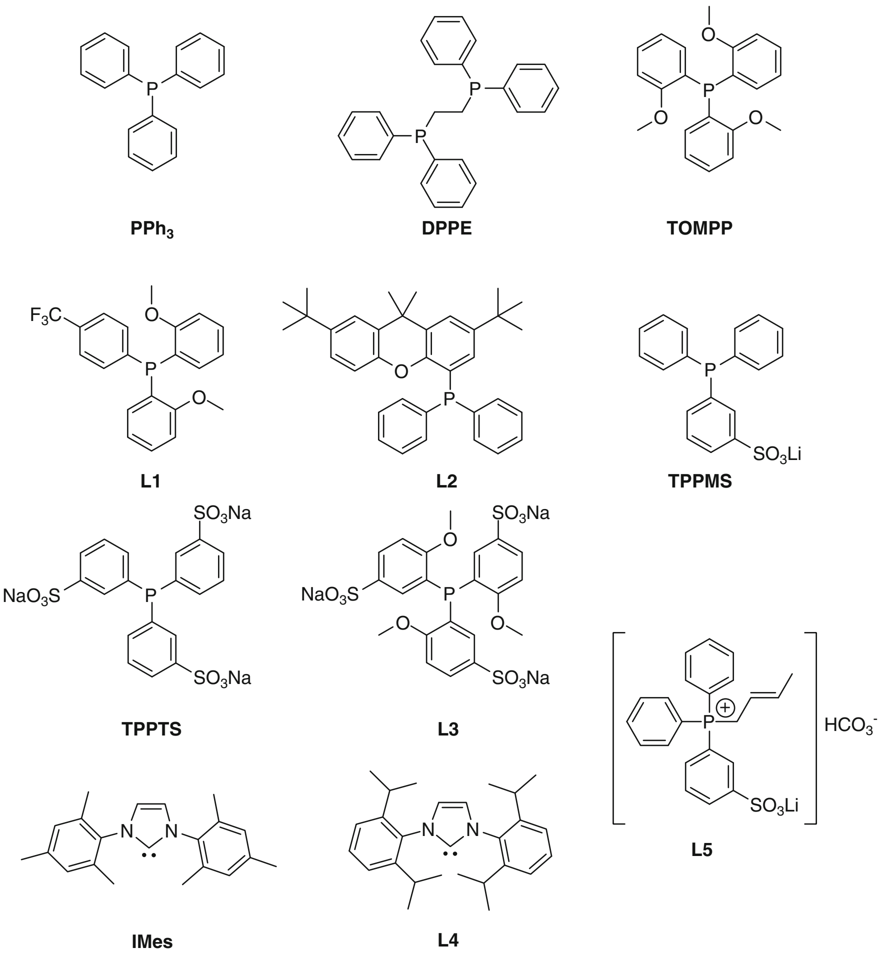


Fig. 2 Some examples of ligands used in the telomerization reaction

The group of Beller puts an emphasis on high activity at very low catalyst concentrations in their evaluation of ligands for the same reaction in order to achieve the TONs necessary for industrial application [31]. At very low catalyst concentrations (0.002 mol%), PPh$_3$ outperformed all other ligands tested with a conversion of 58% and a TON of 30,500. Palkovits et al. assessed the performance of different phosphines in the transformation of bulky nucleophiles such as glycerol to find the tris(*o*-methoxyphenyl)phosphine (TOMPP) ligand to be very efficient [32, 33]. A recent patent awarded to Dow describes a number of ligands related to TOMPP, of which bis(2-methoxyphenyl)(4-(trifluoromethyl)phenyl)phosphine (L1) was found to be the most active in the telomerization of 1,3-butadiene with methanol [34]. Another recent Dow patent describes bulky phosphines based on

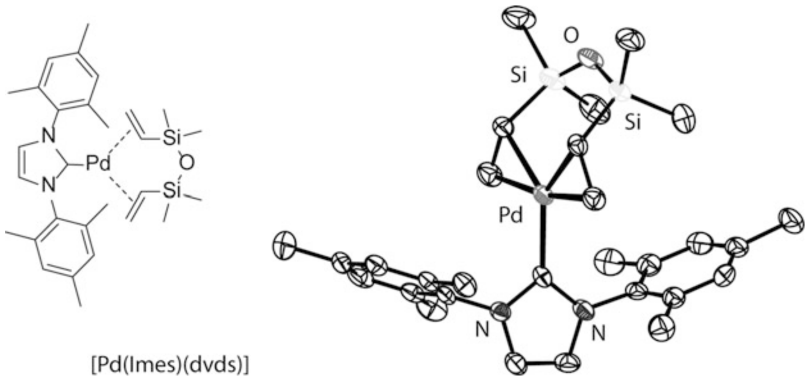


Fig. 3 Chemical structure and X-ray crystal structure of the divinyldisiloxane palladium(0) carbene complexes as synthesized by Jackstell et al. Ellipsoids are drawn at 30% probability, and hydrogen atoms are omitted for clarity [38]

xanthenes for the same reaction; the most active example is 4-(diphenylphosphino)-2,7-di(*tert*-butyl)-9,9-dimethyl-9H-xanthene (L2) [12, 35].

The use of water-soluble phosphines, such as lithium bis(phenyl)(3-sulfonatephenyl)phosphine (triphenylphosphine monosulfonate, TPPMS) or trisodium tris(3-sulfonatephenyl)phosphine (triphenylphosphine trisulfonate, TPPTS), has also been extensively investigated. The reason for this is that the commercially important telomerization with water typically occurs as a two-phase reaction, with the telomer products primarily in the organic phase. It is therefore beneficial to retain the catalyst in the aqueous phase so that the catalyst can be recycled. In a patent awarded to Kuraray, the use of phosphonium salts such as [lithium (2-butenyl)bis(phenyl)(*meta*-sulfonatophenyl)phosphate][hydrogen carbonate] (L5) is described as a non-conventional ligand source. While typically a low P/Pd ratio is needed for optimal activity, leaching of the phosphine into the product phase can also lead to deactivation in a continuous process. The phosphonium salt serves as reservoir for fresh ligand to offset leaching of the catalyst so that the actual ligand/Pd ratio in the reaction remains close to the optimal value [36]. The role of phosphonium species is more extensively discussed in Sect. 3, dealing with the mechanistic aspects of the telomerization reaction.

The novel catalyst system based on palladium(0) *N*-heterocyclic carbene complexes was developed by the group of Beller, in part prompted by the strong patent position of Dow on phosphine-based palladium catalysts [8]. The catalyst [37], either generated in situ from the corresponding imidazolium salt or the molecularly defined divinyldisiloxane complex [Pd(Imes)(dvds)] (Fig. 3), was used in the telomerization of 1,3-butadiene with methanol [38–40]. The *N*-heterocyclic carbenes are in general better σ-donor ligands and come with considerably different steric requirements than the phosphines. The [Pd(Imes)(dvds)] complex resembles the final telomer–palladium product complex and thus offers a facile and clean entry into the catalytic cycle. The metal carbene complex was shown to be highly active, providing conversions up to 97% at only 0.0005 mol% Pd (relative to 1,3-butadiene) with exceptional TONs of up to 1,500,000 and TOFs of around 100,000 h^{-1} [40]. Another advantage of the carbene complex is a very high selectivity towards the linear telomer: typical linear/branched ratios of 39:1 are found for the carbene, compared to 14:1 for PPh_3. The carbene complex was also shown to be active for a large number of other nucleophiles, including isopropanol, 1-butanol, benzyl alcohol, phenol and ethylene glycol [40]. An overview of the historic development of the use of *N*-heterocyclic carbenes in telomerization reactions up to the point of industrial application on a multi-ton scale by Evonik Oxeno is available [8].

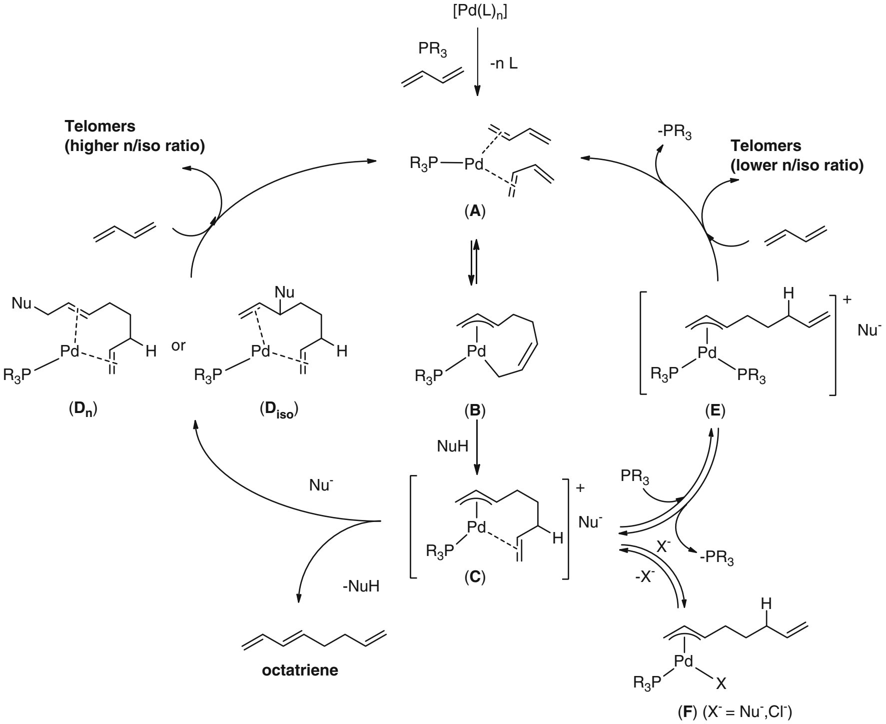
3 Mechanistic Aspects of the Telomerization Reaction

3.1 General Telomerization Mechanism

Before we turn our attention to the various examples of the use of multifunctional nucleophiles in the telomerization reaction, a review of the key aspects of the telomerization mechanism is essential. The discussion of the mechanism is focused on the phosphine-based catalyst systems. The mechanism for carbene-based systems is largely the same, though some important differences exist and will be pointed out. A number of studies, particularly the work of Jolly and co-workers in the 1980s and later by the group of Beller, have led to the elucidation of mechanistic details of the Pd-catalyzed telomerization reaction. In the 1980s, Jolly et al. managed to characterize and in some cases isolate a number of intermediates that allowed them to construct a mechanism for the reaction that explains most of the salient features of the reaction. Beller et al. later extended the mechanistic cycle by suggesting a complementary, bis-phosphine path to account for the certain observations regarding regioselectivity. The generally accepted mechanism is shown in Scheme 4. Recently, these experimental studies have been complemented by computational ones [41, 42].

The reaction is catalyzed by Pd(0) complexes, but the pre-catalyst can be either a Pd(0) or a Pd(II) compound that is to be reduced in situ. Oxidative coupling of two butadienes coordinated to a Pd(0) species of the phosphine ligand (species **A**, Scheme 4) results in the formation of intermediate [Pd(1,2,3,8-η^4-octa-2,6-diene-1,8-diyl)(L)] (**B**). This oxidative coupling is rather facile and reversible; the latter illustrated by the fact that **B** is only stable at high butadiene concentration. Subsequent protonation of **B** by NuH at the 6-position of the η^3,η^1-octadienyl ligand leads to [Pd(1,2,3,7,8-η^5-octa-2,7-dien-1-yl)(L)]Nu (**C**). The complex of type **C** is a pivotal intermediate as several reaction pathways are available from here.

First and most importantly, direct attack of the nucleophile is possible at both the 1- and 3-position of the η^3,η^2-octadienyl chain, which leads to the product complexes [Pd(L)(2,3,7,8-η^4-1-Nu-2,7-octadiene)] (**D$_n$**) and [Pd(L)(1,2,7,8-η^4-3-Nu-1,



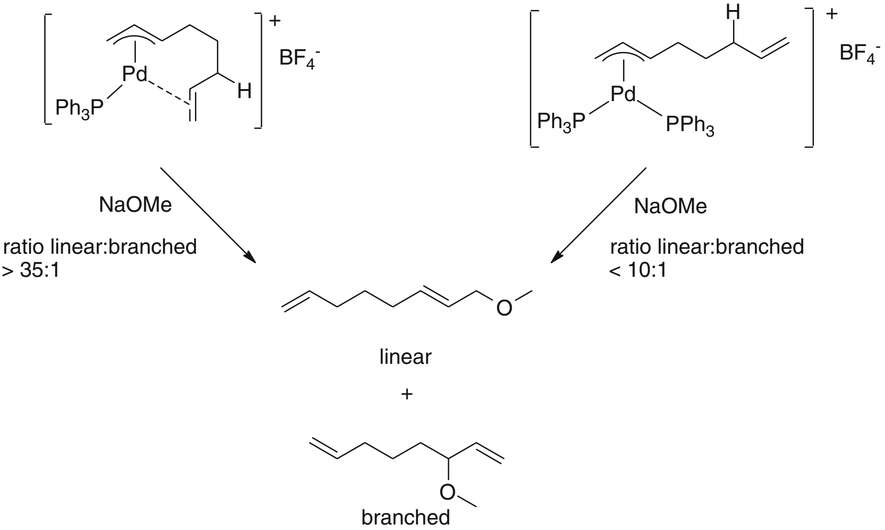
Scheme 4 Catalytic cycle of the Pd/Phosphine-catalyzed telomerization of 1,3-butadiene with nucleophile NuH

7-octadiene)] (**D_{iso}**), respectively. Fresh 1,3-butadiene can then displace the η^2,η^2-octadiene ligand to yield the linear telomer from complex **D_n** and the branched telomer from complex **D_{iso}**. It has been found, however, that there is a considerable difference in reactivity between the 1- and 3-positions in the monophosphine complex **C**, with the formation of **D_n** dominating. This preference for attack at the 1-position, giving rise to a telomer mixture with a high linear/branched ratio, can be attributed to an interplay of steric and electronic effects. In general, the regioselectivity of nucleophilic attack is well-known to be very sensitive to the coordination sphere around the metal in allylic substitution reactions and will heavily depend on the exact nature of the ligands positioned *trans* to the allyl group [1]. Nucleophilic attack at the C1-position is clearly sterically favored. The electronic effect is less straightforward, however, and will depend on the σ-donor/π-acceptor characteristics of the phosphine ligand compared to the coordinated olefin, as these *trans* ligands will influence the electron density and relative cationic charge on C1 and C3 [43–45]. Beller et al. [46] attributed the high linear/branched ratio observed for complexes of type **C** to the energetically more favored formation of **D_n**. The authors reasoned that attack at C1 (linear product) will give rise to a (1,6-diene) palladium complex, which is considerably more stable than the

1,7-diene structure that is obtained by attack at C3 (branched product). It is important to note, however, that the reaction is under kinetic control, with the nucleophilic attack being the rate-determining step. Therefore, differences in activation energy barriers between linear and branched telomer formation are expected to control the regioselectivity of the process rather than differences in thermodynamic stability of the products. Jabri and Budzelaar recently corroborated the experimental observations by a detailed DFT study in which they indeed found the $\mathbf{D_n}$ product to be more stable, the nucleophilic attack to be rate-limiting and the formation of the linear isomer kinetically favored [42]. As nucleophilic attack is often the rate-determining step of the reaction, a strong base or excess amine is often added to enhance nucleophilicity and to speed up the reaction.

Alternatively, coordination of excess phosphine to complex **C** can result in the bis-phosphine complex [Pd(1,2,3-η^3-octa-2,7-dien-1-yl)$(L)_2$]Nu (**E**). The importance of this route was illustrated by Beller et al. for triphenylphosphine and methanol as the telogen. It has to be noted here that the extent of de-chelation of the olefin to give the bis-phosphine complex will be highly dependent on the electronic and steric properties of the phosphine used. This alternative route is important as it results in a lower linear/branched ratio (vide infra), thus negatively influencing the regioselectivity of the reaction. The two competitive pathways explain the influence and critical importance of the P/Pd ratio used in catalysis, as enough phosphine ligand needs to be added to stabilize the catalytic palladium(0) species and to prevent formation of palladium black. Too much phosphine on the other hand will shift the equilibrium to the bis-phosphine complex at the expense of a lowered selectivity. It should be mentioned here that for most substrates, the outcome of the telomerization reaction is kinetically rather than thermodynamically controlled, meaning that the relative importance of the available route determines the composition of the product slate. Note that the bis-ligated route is not well accessible for catalysts with bulky *N*-heterocyclic carbenes, explaining the high regioselectivities obtained with these catalysts. Nucleophilic attack on **E** followed by coordination of fresh 1,3-butadiene once again yields the telomer products. The difference in reactivity between the 1- and 3-positions is much smaller in the bis-phosphine complex, with the formation of the branched telomer becoming less unfavorable as a result. Beller and co-workers illustrated this by reacting the pure mono-phosphine complex and the bis-phosphine complex with the methoxide nucleophile to obtain linear/branched ratios of >35:1 and <10:1, respectively (Scheme 5) [46]. Thus, the balance between these two pathways ultimately determines the ratio of linear and branched telomers in the products. DFT calculations on intermediates of type **E** have also corroborated these results [41, 42].

Soft nucleophiles or halide ions may also coordinate to **C** to give [Pd(1,2,3-η^3-octa-2,7-dien-1-yl)(X)(L)] (**F**) ($X = Nu^-, Cl^-$), which is known to be less active [47] and may even lead to catalyst deactivation. Finally, the by-product 1,3,7-octatriene can also be formed from intermediate **C**, by proton abstraction at the 4-position of the η^3,η^1-octadienyl ligand. Note that the proton that is lost upon 1,3,7-octatriene formation is different from the proton added by the nucleophile (4 position vs. 6 position, respectively), which points at the general irreversibility of the step going from **B** to **C**.

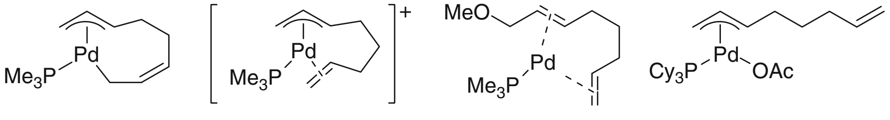


Scheme 5 Regioselectivity differences for mono- and bis-phosphine complexes as observed by Volmüller et al. [46]

Generally, octatriene formation is favored by higher temperatures, higher phosphine and/or butadiene concentrations and, importantly, by an increase in steric bulk of either the ligand or the nucleophile. Indeed, Harkal et al. showed a selectivity switch from telomerization products to 1,3,7-octatriene formation by altering the steric demand of the *N*-heterocyclic carbene ligand in the reaction of butadiene with isopropanol under further identical reaction conditions [48]. For the more basic nucleophiles, such as the alcohols, the telomer products are stable under experimental conditions, i.e. product formation is irreversible, but for more acidic substrates such as phenol, product formation is reversible and more 1,3,7-octatriene will be formed after the substrate has been depleted.

Jolly and co-workers thoroughly investigated the Pd-catalyzed reactions of 1,3-dienes and provided much of the basis for the present understanding of the catalytic cycle of Pd-catalyzed telomerization reaction depicted above [47, 49–52]. Several intermediates were observed in solution, and their dynamics were studied using NMR spectroscopy and some even isolated, as complexes of type **B** could, for instance, be studied by single crystal X-ray diffraction.

The intermediates of type **B** could be prepared from [Pd(η^3-allyl)$_2$] by reacting the precursor with 1,3-butadiene in the presence of a donor ligand. Characterization by NMR and single crystal X-ray diffraction of [Pd(1,2,3,8-η^4-octa-2,6-diene-1,8-diyl)(PMe$_3$)] $\mathbf{B_1}$ (Figs. 4 and 5) demonstrated that the bis-allyl is bound in a η^1,η^3 configuration and did not rearrange to the η^3,η^3 configuration up to the complex's decomposition temperature (at −25°C) [47]. This is different from the analogous Ni compound, which does form an η^3,η^3 chelate [54]. The crystal structure of a complex of type **B** derived from the 1,3-diene allylidene cyclopropane has also



$\mathbf{B_1}$ $\mathbf{C_1}$ $\mathbf{D_1}$ $\mathbf{F_1}$

Fig. 4 Catalytic intermediates as first prepared and identified by Jolly and co-workers

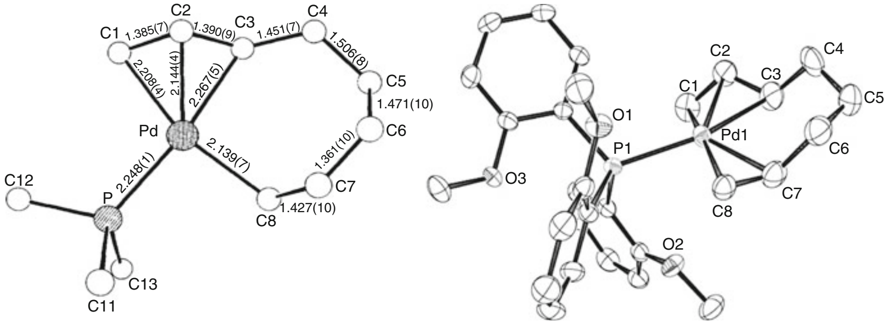
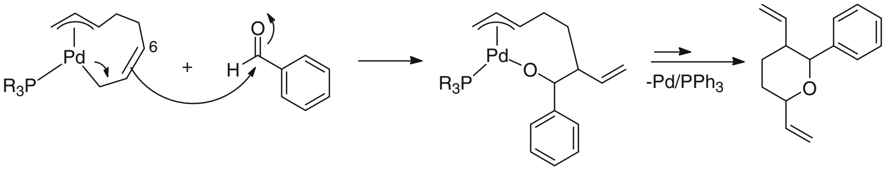


Fig. 5 Crystal structures of a type **B** complex [Pd(1,2,3,8-η^4-octadiene-1,8-diyl)(PMe_3)] (*left*) and type **C** complex [Pd(1,2,3,7,8-η^5-octa-2,7-dien-1-yl)(tris(2-methoxyphenyl)phosphine)]BF_4 (*right*). The BF_4^- anion and hydrogen atoms are omitted for clarity [51, 53]

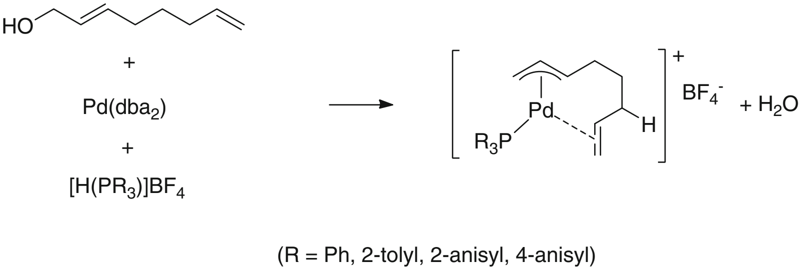
been reported [55]. Reaction of the complex $\mathbf{B_1}$ with methanol yielded [Pd(2,3,7,8-η^4-1-methoxy-2,7-octadiene)(PMe_3)] $\mathbf{D_1}$, which was identified by NMR spectroscopy. It was also shown that the product could be displaced by fresh 1,3-butadiene to yield the original η^3,η^1-octadienediyl complex and the telomer product, demonstrating that these complexes can form a complete catalytic cycle [51].

Upon addition of a NuH, such as during the reaction from $\mathbf{B_1}$ to $\mathbf{D_1}$**,** the key intermediate [Pd(1,2,3,7,8-η^5-octa-2,7-dien-1-yl)(PMe_3)]$^+$ ($\mathbf{C_1}$) of type **C** was also observed. The BF_4^- and PF_6^- salts of $\mathbf{C_1}$ could also be prepared by reacting $\mathbf{B_1}$ with HBF_4 or HPF_6 and were characterized by ^{1}H-NMR spectroscopy [47]. Performing the telomerization with CD_3OD yielded the telomer product exclusively deuterated at the sixth carbon atom, providing evidence for the basicity of this position [52]. The nature of the nucleophilic anion after deprotonation of NuH is important, as the reaction of $\mathbf{B_1}$ with acetic acid resulted in the isolation of the **F**-type complex [Pd (1,2,3-η^3-octa-2,7-dien-1-yl)(OAc)(PCy_3)] ($\mathbf{F_1}$) rather than $\mathbf{C_1}$. This demonstrates that strongly coordinating ligands such as acetate may play an important role in catalyst deactivation [47]. The versatility of the intermediates was shown by the analogous reactions with isopropanol, acetic acid, malonitrile, diethyl malonate, methyl 2-cyanoacetate and 2-hydroxy-2-phenylacetic acid [51].

The amphiphilicity and in particular the nucleophilic character of carbon atom C6 of the octadienyl chain in the η^3,η^1-bis-allyl complexes of type **B** was clearly demonstrated by Tsuji and co-workers [56, 57], who showed that reacting benzaldehyde with 1,3-butadiene in the presence of a Pd catalyst and PPh_3 ligand yields



Scheme 6 The nucleophilic character of C_6 in the η^3,η^1-bis-allyl complex is exemplified by reaction with electrophilic benzaldehyde to yield the co-cyclization divinylpyran product

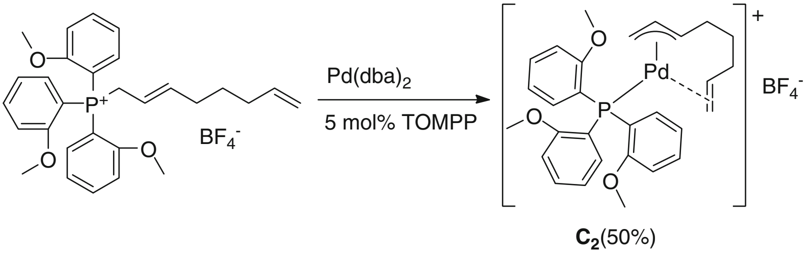


Scheme 7 Preparation of complexes of type **C** as reported by Hausoul et al. [53]

the cyclization product 2-phenyl-3,6-divinyltetrahydro-2*H*-pyran. This product is formed by nucleophilic attack of the C6 carbon atom on the C=O double bond of benzaldehyde, followed by an intramolecular ring-closing reaction with the η^3-allyl as shown in Scheme 6. This co-cyclization of butadiene with C=O or C=N bonds is another general route that can be followed under telomerization conditions. Related to this, the nucleophilic nature of the σ-bound η^1-allyl group in **B** has also been invoked to explain the formation of some higher C16-telomers, resulting from a coupling between two intermediates **B** and **C**, observed by Parvulescu et al. for a heterogenized Pd/TPPTS catalyst (vide infra, Sect. 3.2) [58].

Recently, a simple and efficient method was reported for the synthesis of complexes of type **C** with various electronically and sterically different phosphines. The method takes advantage of the reversibility of product formation under acidic conditions, by reacting $Pd(dba)_2$ with the relevant $[H(PR_3)]BF_4$ salt and 2,7-octadienol (Scheme 7) [53]. The structures of the intermediates with the ligands triphenylphosphine and tris(*ortho*-methoxyphenyl)phosphine (TOMPP) were determined by X-ray crystallography, providing conclusive evidence for the η^3,η^2 coordination of these complexes. The reactivity of the complexes with five different phosphine ligands towards to methoxide anion was monitored by UV-Vis spectroscopy, and large differences in relative rate were observed, illustrating the influence that both the steric and electronic properties of the phosphine exert on **C**.

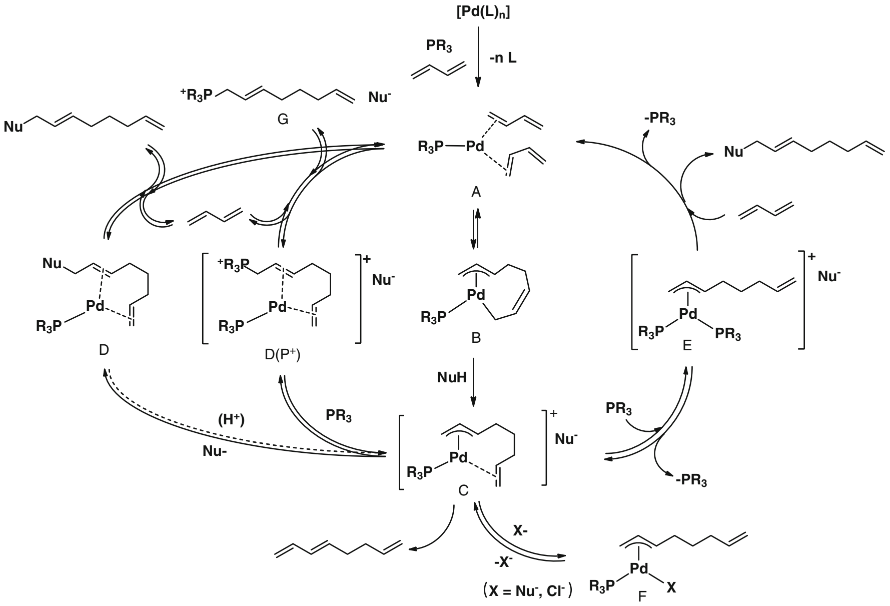
It is clear from the above that several undesired pathways are available that can hamper one's aim of obtaining the highest selectivity for the linear telomer product. In addition, most of the steps involved in the cycle are fully reversible under the proper conditions, and the outcome of the reaction, selectivity as well as catalyst stability,



Scheme 8 Reversibility of phosphonium formation, as evidenced by Hausoul et al. for the Pd/TOMPP system [59]

is therefore highly dependent on the extent to which these equilibria can be controlled. Indeed, as stated before, for many telogens, the telomerization is under kinetic control, as product formation is often not reversible under the basic conditions employed (in some cases, e.g. with phenol, the reaction can proceed under thermodynamic control, though). In this light, it is important to discuss another reversible reaction that influences the outcome of the reaction, in particular in terms of catalyst deactivation. Hausoul et al. have recently pointed at a correlation between the extent of telomerization of the phosphine itself, i.e. phosphonium formation [59], and the substrate-dependent deactivation that was observed with glycerol and various sugars and sugar alcohols [60]. Analysis of the post-catalytic reaction mixtures revealed that for substrates for which rapid deactivation was observed (e.g. the hemi-acetal fructose), up to 99% of the phosphine was converted to a phosphonium salt, whereas for substrates that showed no apparent deactivation (e.g. glycerol), only about 33% of the phosphine was found to be alkylated. This in situ formation of the phosphonium salt was previously reported by Maddock et al. in the telomerization of isoprene with dimethylamine. As the phosphonium salt could not be reacted with dimethylamine by incubation, the authors concluded that phosphonium formation was not reversible and that the species did not participate in the catalytic cycle. In contrast, in both patents from the Kuraray company [61–63] and a contribution from the group of Behr [64], phosphonium salts of TPPTS were actually deliberately added to the reaction mixture to serve as ligand reservoirs in the biphasic telomerization of butadiene with water. This implies reversibility and a more prominent role for the phosphonium species. Hausoul et al. subsequently showed that phosphonium formation is fully reversible, at least in case of the TOMPP ligand, as the tris(2-methoxyphenyl)(2,7-octadienyl)phosphonium tetrafluoroborate salt could be readily converted back to the intermediate **C** (**C$_2$**) with Pd(dba)$_2$ and, importantly, a catalytic amount of TOMPP (5 mol%). A conversion of about 50% was achieved, pointing at an 1:1 equilibrium between the phosphine and phosphonium under these conditions (Scheme 8).

This, together with the observations by other authors, shows that phosphonium formation is a general aspect of the telomerization reaction and can be added as another reversible side reaction that is available for complex **C**. This extended



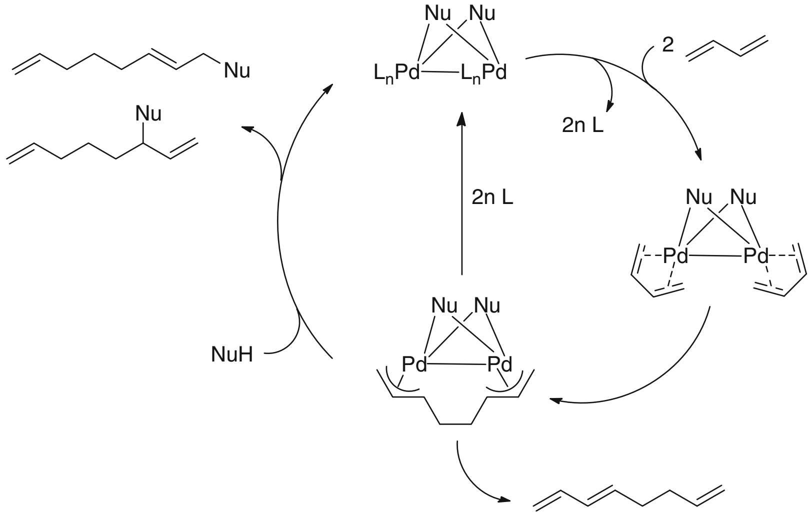
Scheme 9 Telomerization mechanism extended with the route that leads to phosphonium formation, adapted from [59]

mechanism, including also the reversibility of product formation under acidic conditions, is depicted in Scheme 9. The importance of the phosphonium route will depend on the particular phosphine used and should be assessed for more cases than TOMPP. An interesting consequence of phosphonium formation is that the associated anion has to be the anion of the nucleophile. Product formation may therefore also be accelerated as the concentration of the nucleophile is thus raised with respect to complex **C**. In the case of TOMPP, this might explain why no additional base is required for high activity (vide infra) [59].

Some authors have proposed mechanisms based on bimetallic palladium species. Keim and colleagues, for instance, proposed a reaction mechanism for the telomerization of acetic acid with butadiene (Scheme 10), where the key intermediate is a bispalladium compound such as [Pd_2(μ-1,2,3,6,7,8-η^6-octa-2,7-dien-1,8-diyl)(μ-OAc)$_2$] [65]. It was shown that these bimetallic compounds are able to catalyse telomerization in the presence of 1,3-butadiene, acetic acid and a phosphine ligand.

3.2 Formation of Higher Telomers

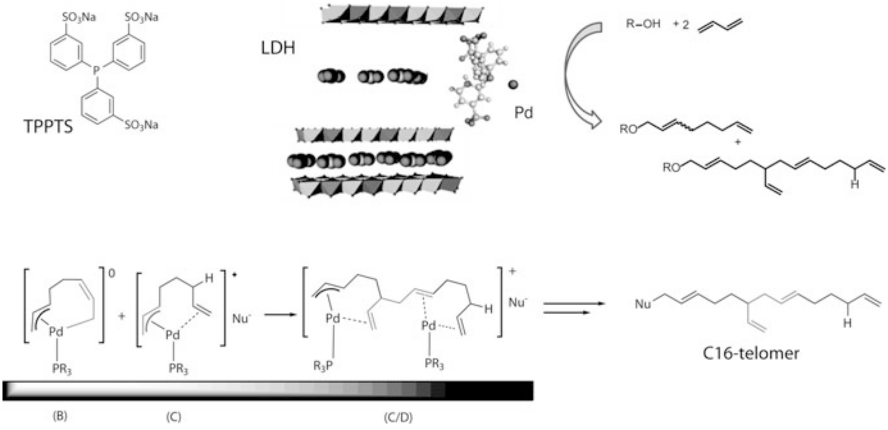
In all examples discussed up to this point, the telomer products have always had two units of the taxogen (e.g. butadiene) incorporated. The group of Tkatchenko [66] nonetheless first observed that under some conditions, telomers with more than two



Scheme 10 Bimetallic telomerization mechanism proposed by Keim [65] for acetic acid or phenol telomerization, adapted from [25]

1,3-butadiene units are formed [67]. In order to explain this, the formation of bimetallic complexes featuring methanol bridges was proposed. However, no experimental evidence for these complexes has been reported to date. Higher telomers were also observed in significant amounts by Parvulescu et al. in the telomerization of butadiene with methanol and ethylene glycol using a Pd/TPPTS catalyst immobilized on a layered double hydroxide support (see also Sect. 4.1.1). An alternative mechanism was proposed to account for the higher telomers [58]. NMR data shows that the higher telomers mainly consist of 6,1′-coupled C8 units, as a result of a C–C coupling reaction between a secondary and primary carbon. This can be explained by the interaction and coupling of the C8 chains of two distinct palladium intermediates, i.e. the η^3,η^1-intermediate **B** and the η^3,η^2-intermediate **C** (Scheme 11).

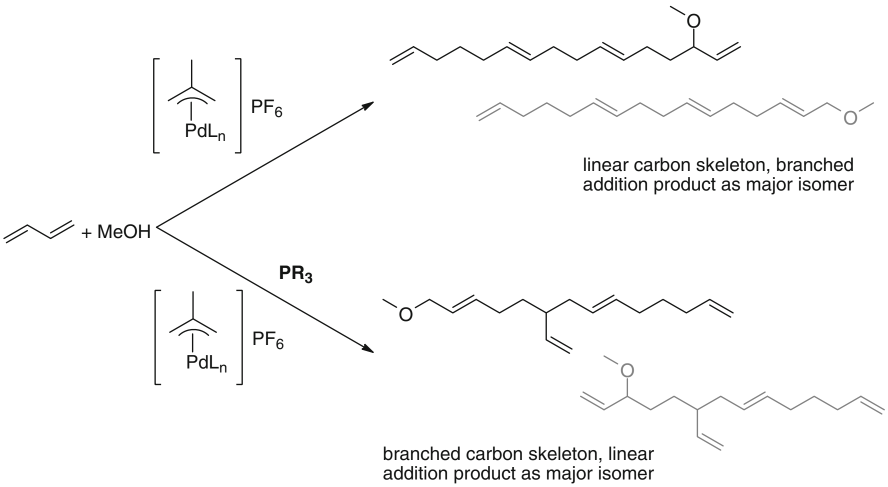
The nucleophilic nature of η^1-allyl palladium groups, such as the σ-allyl group in **B**, is well documented [68]. Indeed, Kiji et al. demonstrated the nucleophilic nature of **B** itself in the telomerization of butadiene with electrophilic reagents, such as benzaldehyde, to give pyran products [57]. These addition reactions are examples of the co-cyclization reactions of butadiene with heteropolar double bonds, as discussed by Tsuji. Other examples of this type of reactivity include the synthesis of divinylpiperidones with isocyanates [56]. Similarly, nucleophilic attack of the σ-allylic group in **B** at the 1-position of intermediate **C** would give C16 telomers with the observed regiochemistry. On the layered double hydroxide that is used as catalyst support in this particular example, the catalyst is localized on the external surface, leading to a high local concentration of Pd/TPPTS species and increased chance of C–C coupling. In addition, the polycationic nature of the brucite layers of the support may trap the conjugate base of ethylene glycol, i.e. the nucleophilic substrate, so that coupling reactions get a chance to occur before the nucleophile is added and the normal telomer product is formed.



Scheme 11 C16 telomer formation by coupling of two C8 chains proposed by Parvulescu et al. for a Pd/TPPTS catalyst immobilized on a layered double hydroxides (LDH)

A few other examples of higher telomer formation have also been reported. In the early 1980s, Grenouillet et al. communicated the use of η^3-allyl palladium complexes to obtain a mixture of C8 and C16 telomers of butadiene and methanol [66]. Interestingly, the use of the C8 telomer as the substrate also gave C16 telomers. A more extensive study later showed that higher telomer selectivity depends on the methanol/butadiene ratio (with an optimum value of 1:2 rather than the expected 1:4), temperature, time and the presence/absence of phosphine donor ligands [67]. Highest selectivities are observed at short reaction times, gradually dropping due to the formation of higher oligomers of butadiene. Interestingly, without phosphine, the major C16 telomer isomer contains a linear C16 chain with the methoxide added preferentially (about 6–10 times more) at the 3-position (i.e. branched) (Scheme 12, top). The addition of phosphines (2 eq. with respect to palladium) leads to a drop in higher telomer formation, with a concomitant switch in regioselectivity. The main product now contains a linear C14 chain with a vinyl substituent at the 6-position and the methoxide added at the 1-position (i.e. the linear isomer) (Scheme 12, bottom). The latter products are the same as those observed by Parvulescu et al. [58]. Based on their results, the authors also propose the coupling of two C8 units to account for the observed C16 telomers. For the linear C16 products, dinuclear palladium complexes held together by methanol/methoxide bridges are again proposed. The change in regioselectivity of the coupling in the presence of phosphines is attributed to the ligands breaking up these dimers. The mechanism proposed by the authors for the Pd/P catalyst seems to involve the coupling of two type **C** complexes, but it is difficult to see how this would actually proceed.

C,*N*-bidentate organometallic complexes showed high selectivity for the higher telomers, with C24 telomers being obtained in one case as the major product. Addition of triphenylphosphine again resulted in a dramatic drop in higher telomer production and increased dimer formation [69]. The branched addition product was identified as the major one for the C16 and C24 telomers, and a linear carbon



Scheme 12 Observed differences in regioselectivity in the formation of higher C16 telomers with allyl palladium catalysts

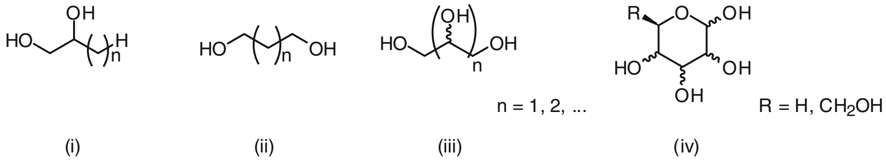
chain is suggested, but no experimental information was given on how this was established. Schuchardt et al. also noted the formation of C16 telomers with methanol if η^3-allyl palladium(II) complexes were used with dibenzylideneacetone as ligand, the branched isomer again being the main product [70]. Finally, Hausoul et al. also observed some C16 telomers with some of the sugar substrates that were tested, albeit in low amounts.

In all cases, the formation of the higher telomers therefore seems to occur in multiples of C8 (i.e. coupling of an even number of butadiene monomers). The regioselectivity differences observed under the different circumstances and with the various catalyst systems are intriguing, and further investigations into the mechanistic details are warranted. Indeed, for some applications, e.g. as surfactant, aliphatic chains longer than C8 are required to get the proper balance in hydrophilicity/hydrophobicity and molecular control over the process that allows one to achieve this is thus highly desired.

4 Telomerization with Biomass-Derived Multifunctional Telogens

4.1 Telomerization with Polyols

The telomerization of butadiene with the simple monoalcohol methanol has been studied extensively; in fact, methanol often serves as the prototypical nucleophile to assess important parameters concerning catalyst activity and selectivity (e.g. linear/

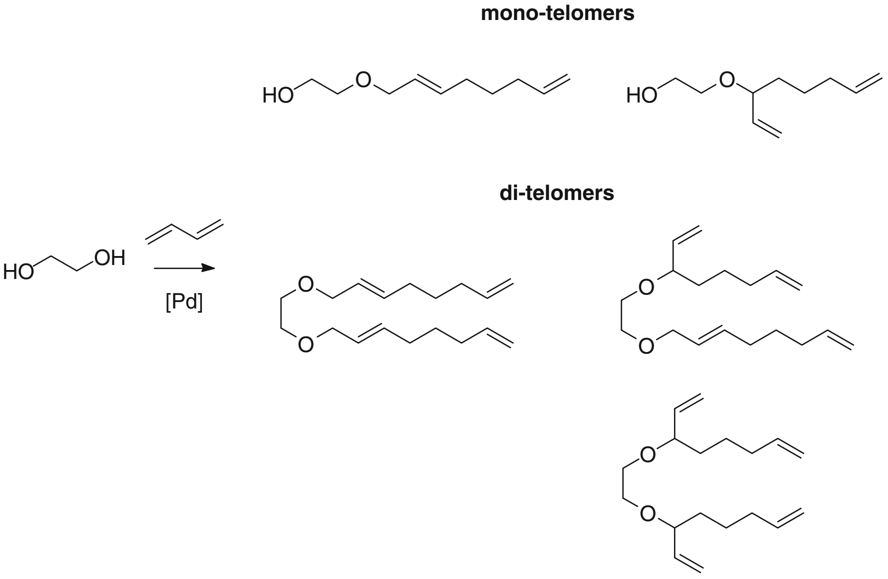


Scheme 13 The four generic formulas for linear polyols relevant to telomerization with 1,3-butadiene: 1,2-diols (*i*), linear diols (*ii*), sugar alcohols (*iii*) and (poly)saccharides (*iv*)

branched ratio). As discussed in the introduction, the telomerization with methanol is the first step in the production of 1-octene by Dow Chemical in their Tarragona plant, presumably using palladium with an aryl phosphine ligand. Beller and co-workers have also reported significant advancements in the telomerization of methanol, using *N*-heterocyclic carbene ligands instead [8]. A few examples that use ethanol have also been reported, evidently readily available from renewable resources, as the telogen [30, 66, 67]. Other examples of monofunctional alcohols with butadiene and other conjugated dienes, isoprene in particular, can be found in the review by Behr et al. [25]. Polyols are an attractive class of substrates as the multifunctional nucleophiles allow different degrees of substitution and with this alteration of the physicochemical properties of the products. The telomerization of some, but not all of the –OH groups, results in products with a polar head group and an apolar tail, making the product amphiphilic and thus very suitable for application in surfactants and emulsifiers. The polyols are readily obtained directly from biomass feedstock or from renewable platform molecules. In general, the polyols used for telomerization can be classified into four groups: (1) 1,2-alkanediols containing both a primary and a secondary alcohol group (glycols, e.g. 1,2-propanediol), (2) linear diols containing two primary alcohol groups (e.g. 1,3-propanediol), (3) the fully substituted sugar alcohols containing both primary and secondary alcohols (e.g. ethylene glycol, glycerol, sorbitol, etc.) and finally (4) the various classes of mono- and polysaccharides (Scheme 13).

4.1.1 Telomerization of Ethylene Glycol

Ethylene glycol (EG) may be obtained from cellulose by many ways, for instance, by the catalytic conversion over carbide catalysts [71]. It is the simplest linear polyol available and often serves as a model for more complex substrates. Many reports are therefore available on the telomerization of EG. The possible telomer products are shown in Scheme 14, the linear mono-telomer typically being the desired compound. The mono-telomer can be used, after saturation of the double bonds, as a plasticizer alcohol in polyvinylchloride production, whereas application in cosmetics and surfactants has also been indicated [72]. Early examples include the work of Dzhemilev et al., who first reported on the telomerization of butadiene with EG in 1980, yielding a mixture of the mono- and di-telomers and butadiene dimers using a palladium catalyst activated by $AlEt_3$ [73]. Kaneda also reported the use of EG in



Scheme 14 Telomer products of ethylene glycol with 1,3-butadiene

their activity screening of polymer-bound palladium(0) complexes with various classes of substrates [74]. The mono-telomer was selectively obtained (89%) with a linear/branched ratio of 13 after 18 h. The reaction was run neat, with a little added benzene to ensure swelling of the polymer. A run with the homogeneous catalyst gave essentially the same selectivity at a somewhat lower overall yield (61%).

Behr and Urschey built on the work by Dzhemilev et al., testing both liquid single phase and biphasic systems. Experimental conditions were first optimized in the single phase reactions, reaching TONs of about 1,500, but mono-telomer selectivity was unsatisfactory for the monophasic Pd/PPh_3 system. Different ligands were tested in addition to PPh_3, including diphosphines and an *N*-heterocyclic carbene (Table 1). Chelating bis-phosphine ligands either increased di-telomer (DPPM) or 1,3,7-octatriene yield (DPPE) or decreased activity altogether (DPPP, DPPB). Use of the *N*-heterocyclic carbene ligand IMes at only 0.02 mol% Pd under the same conditions resulted in an extremely active catalyst and gave an EG conversion of 93%, but at the expense of a 41% yield of butadiene dimers. Alkyl phosphines ($P(n\text{-}Bu)_3$, PCy_3) or phosphites ($P(OEt)_3$, $P(OPh)_3$) did not provide satisfactory telomer yields. The standard catalyst system $Pd(acac)_2/PPh_3$ furthermore fails to convert the pure mono-telomer, illustrating the fact that this is a rather poor nucleophile. The catalyst with the NHC ligand, in contrast, does directly convert the pure mono-telomer. As concentration profiles show that the mono- and di-telomer are formed simultaneously, the authors invoke a second catalytic cycle in which the mono-telomer remains coordinated to palladium to explain the rather high amounts of di-telomer obtained also with PPh_3.

Table 1 Selected results of the telomerization of 1,3-butadiene with ethylene glycol for optimized systems as reported by Behr et al. [72]

Ligand	[Pd] (mol%)[a]	THF (mL)	H_2O (mL)[b]	Yield (%)			TON	TOF (h^{-1})
				Mono-telomers[a]	Di-telomers[a]	Octatriene[c]		
PPh_3	0.06	5	0	53	18	6	1,204	602
DPPM	0.06	5	0	57	25	7	1,388	694
DPPE	0.06	20	0	56	16	18	1,223	611
DPPP	0.06	15	0	44	5	4	820	410
DPPB	0.06	15	0	22	1	2	389	195
IMes[d]	0.02	0	0	51	41	1	4,299	2,150
TPPTS[e]	0.06	0	10	80	<0.5	<1	1,356	339
IMes[d,f]	0.02	0	5	14	48	2	2,889	963

Conditions: 1,3-butadiene/ethylene glycol ratio 2.5; $Pd(acac)_2$ + ligand, P/Pd or NHC/Pd ratio 2; 2 h, 80°C, stirring at 800 rpm; *DPPM* bis-(diphenylphosphino)methane, *DPPP* bis-(diphenylphosphino)propane, *DPPB* bis-(diphenylphosphino)butane

[a] Based on ethylene glycol

[b] Stirring in biphasic system at 1,200 rpm

[c] Mass percentage of 1,3,7-octatriene in the reaction mixture

[d] Generated in situ from IMesCl

[e] Reaction time 4 h, P/Pd = 5

[f] Reaction time 3 h; 1 mol% NaOH based on 1,3-butadiene was added

Inspired by the work of the group of Keim on the suppression of consecutive reactions by using aqueous biphasic catalysis [75], as exemplified in the telomerization of butadiene with ammonia, the authors also performed the same reaction in a biphasic system using the water-soluble TPPTS ligand [72]. Activity was considerably lower (TOF 339 h^{-1} vs. 602 h^{-1} for PPh_3), but the selectivity towards the mono-telomer increased dramatically to >99%, with a yield of 84% after 4 h of reaction. By-products such as di-telomers, 1,3,7-octatriene or 2,7-octadien-1-ol were formed but in very limited amounts (<1%). The linear/branched ratio was comparable to that typically observed for PPh_3 (9:1). The remarkable selectivity of the biphasic TPPTS system can be explained by the fact that the Pd/TPPTS complex is highly water soluble and thus remains in the aqueous phase. On the other hand, the solubility of the mono-telomer product in the aqueous phase is fairly low: the local concentration of ethylene glycol thus remains many times higher than that of the mono-telomer, preventing formation of di-telomers. At the same time, the solubility of 1,3-butadiene in the aqueous phase is also poor, limiting the activity of the system. With the catalyst and product in separate phases, this also enables easy recycling of the catalyst, although fresh ligand had to be added after each run to maintain activity. In this way, the catalyst could be recycled six times, for a total turnover number of 8,473.

The biphasic system was further improved by running the EG telomerization in a three-step mixer settler set-up, to overcome issues with the diminished rate arising from mass transport limitations. The process was run for 30 h with a 75% yield of mono-telomer and palladium leaching limited to only 19 ppm [76].

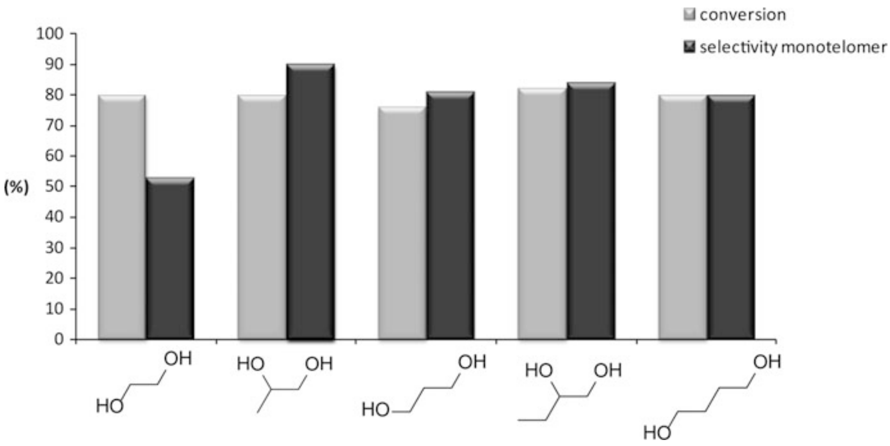


Fig. 6 Conversion and selectivity of the Pd/TOMPP-catalyzed telomerization with various diols [77]

Weckhuysen and co-workers explored the solventless, single phase telomerization of EG using the ligand TOMPP (Fig. 6). TOMPP had previously given the best results in a ligand screening study for glycerol telomerization (vide infra) [77]. The Pd/TOMPP system showed the highest activity with 80% conversion after 66 min at 80°C, using only 0.01 mol% Pd (relative to ethylene glycol) and a 1,3-butadiene/ethylene glycol ratio 2. However, as previously observed by Behr for the monophasic systems, selectivity was rather low at 53% with a mono-telomer yield of 42% and di-telomer yield of 38%.

The group of Beller [39, 78] also investigated the telomerization of 1,3-butadiene with ethylene glycol. Several ligands were screened, including IMes, the more sterically demanding carbene L4, PPh_3 and TOMPP, for activity at a Pd concentration of 0.001 mol% (Fig. 2, Table 2). IMes was found to be most active, providing 98% conversion of 1,3-butadiene after 16 h. Interestingly, the counter-anion from the imidazolium salt used as ligand precursor was not at all innocent and had a significant effect on the overall activity. The more bulky carbene gave a conversion of only 59% of 1,3-butadiene, while of the two phosphines tested, TOMPP clearly gave the best results with a 1,3-butadiene conversion of 81%. The superior activity of the carbene ligands was illustrated by further lowering the palladium loading to only 2 ppm. Under these conditions, the phosphine-based systems proved ineffective, yet the carbene-based catalyst demonstrated still excellent activity with TONs of up to 255,000.

Parvulescu et al. noted an interesting change in EG telomer product selectivity upon immobilization of an Pd/TPPTS catalyst on a basic support [58]. In an attempt to address the issues associated with recovery and reuse of the telomerization catalyst, the anionic TPPTS ligand was immobilized on various layered double hydroxides by ion exchange methods (Scheme 11). The use of these catalysts in the telomerization of methanol and ethylene glycol resulted in a remarkable shift in

Table 2 Selected results of the ligand screening for the Pd-catalyzed telomerization of 1,3-butadiene with ethylene glycol by Grotevendt et al. [78]

Ligand	Yield (%)[a]			TON
	Mono-telomers	Di-telomers	Octatriene	
IMes[b]	63	33	2	95,900
IMes[c]	24	2	0	25,900
L4[b]	46	9	4	54,900
PPh_3	38	6	12	43,900
TOMPP	58	21	2	78,900

Conditions: 1,3-butadiene/ethylene glycol ratio 2, 0.001 mol% [Pd], 0.5 mol% $NaOCH_2CH_2ONa$; ligand/Pd ratio 10; 16 h, 80°C, THF 15 mL

[a] With respect to 1,3-butadiene

[b] Prepared in situ from the corresponding imidazolium chloride

[c] Prepared in situ from the corresponding imidazolium bromide

selectivity from the classical C8 telomers to higher telomers containing mostly C16 carbon chains. A selectivity of up to 48% is reported for higher telomers of EG, which consist for >90% of C16 telomers. The higher telomers are thought to originate from a coupling reaction between two distinct intermediates of the catalytic cycle (**B** and **C**). The mechanistic aspects and other examples of higher telomer formation are discussed in detail in Sect. 3.2.

4.1.2 Telomerization of Other 1,2- and Linear Diols

Several of 1,2-diols and linear diols other than ethylene glycol have also been tested in the telomerization reaction, particular examples include 1,2,- and 1,3-propanediol, 1,2- and 1,4-butanediol and higher homologues. These compounds can be obtained from renewable resources through various routes. The hydrogenation of lactic acid under mild conditions to 1,2-propanediol has long been known, for instance [79]. Likewise, 1,3-propanediol [80] and 1,4-butanediol [81] may be obtained from corresponding three or four carbon lactones or esters or through biological routes [82]. Dupont's Sorona® (a polytrimethylene terephthalate) and Cerenol™ (polyether polyol) polymers are made of fully renewable 1,3-propanediol and illustrate the viability of these latter routes.

Behr et al. [83] also tested the linear diols 1,3-propanediol and 1,4-butanediol under the aqueous biphasic conditions described above. Yields of up to 60% could be obtained for 1,3-propanediol, but conversion dropped considerably as a yield of 31% was recorded for 1,4-butanediol. The TOFs for ethylene glycol (339 h^{-1}) and 1,4-butanediol (134 h^{-1}) obtained under identical conditions clearly reflect the drop in activity upon elongation of the carbon chain. Palkovits et al. observed a different trend when they tested various diols under monophasic conditions (Figs. 6 and 7). Reaction conditions were optimized for 1,3-propanediol (butadiene/substrate ratio of 2:1, 353 K, 0.01 mol% Pd, TOMPP/Pd 5:1) giving the mono-telomer in 61% yield and 81% selectivity at 76% conversion with a TOF of around 21,000 h^{-1}.

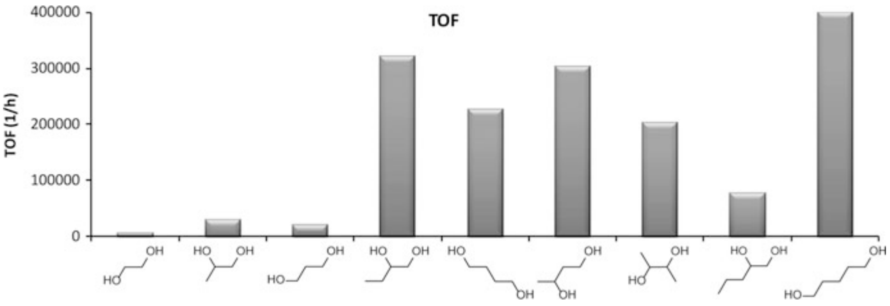


Fig. 7 TOFs determined at low conversion for various diols using the Pd/TOMPP catalyst under solventless conditions [77, 84]

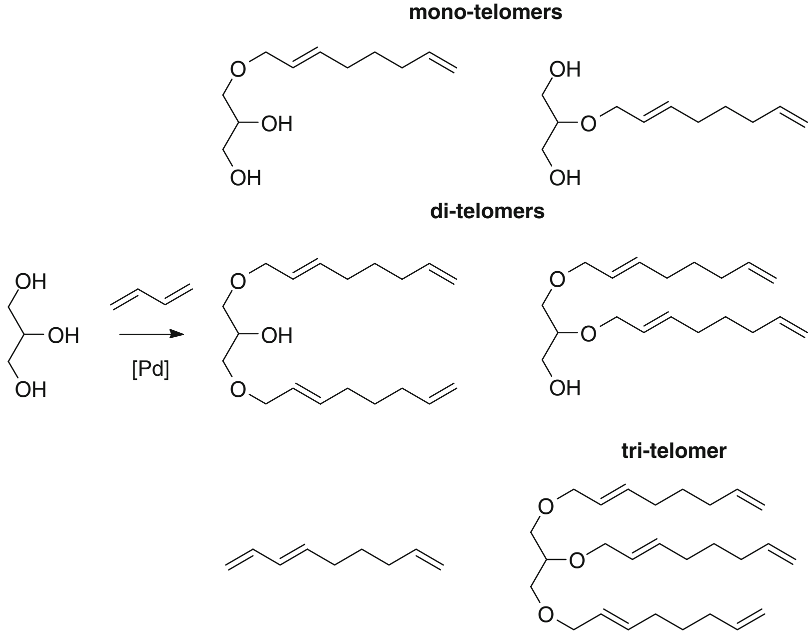
In contrast to the results reported by Behr under biphasic conditions, the activity of the system increased considerably with the longer-chain alcohols, going from an initial turnover frequency of 7,200 h^{-1} for ethylene glycol to 321,000 h^{-1} for 1,2-butanediol. This remarkable increase in activity was attributed to the increased hydrophobicity and the resulting better solubility of the diol in 1,3-butadiene, where the ligand is preferentially found. In addition, the yield of di-telomers was remarkably lower than for ethylene glycol. The highest TOF recorded for diols under these conditions was 400,000 h^{-1} for 1,5-pentanediol [84].

The catalyst system with the 1,3-dimesitylimidazolium chloride ligand (IMes) that worked exceptionally well for ethylene glycol [78] also worked well for the conversion of 1,3-propanediol, 1,3- and 1,4-butanediol and 1,4-pentanediol. Chemoselectivities for the mono-telomer are in the range of 74–94%. Somewhat surprisingly, the conversion found for 1,3-propanediol was lower than for either ethylene glycol or 1,4-butanediol.

In all reported examples on the diols, the primary alcohols were found to react faster than the secondary ones, as expected and previously shown for telomerization of monofunctional alcohols [40]. The improved selectivity for the mono-telomer over the di-telomer observed for most of the non-linear diols over the linear ones can be attributed to this difference in reactivity.

4.1.3 Telomerization of Glycerol

Given its ready availability and chemical versatility, glycerol has a lot of potential to become a primary building block in future biorefineries. It is produced as the major by-product in the production of biodiesel, which conventionally involved the base-catalyzed methanolysis of triglycerides. This process yields about 110 kg of crude glycerol per 1 ton of biodiesel produced. The mandated increase in production of biodiesel has concomitantly led to increased amounts of glycerol flooding the market. It is therefore not surprising that this has spurred much interest in finding new (catalytic) routes for the valorization of glycerol. The volatility of the glycerol



Scheme 15 Palladium-catalyzed telomerization of butadiene with glycerol. The branched products have been omitted for clarity

price has dampened this initial interest to a certain extent, but has not limited the inherent potential of glycerol to play a major role as renewable building block.

The new applications are to be found outside the traditional commercial applications of glycerol in food additives, pharmaceuticals, cosmetics and personal care products and also various industrial applications, such as the synthesis of polyethers, polyols and alkyd resins, detergents, explosives, etc. [85]. The use of low-quality glycerol from biodiesel production for these applications is often avoided, however. Additional fields of applications as a C3 building block have been widely investigated and in a few cases even commercialized, e.g. the production of epichlorohydrin via the EPICEROL® process of Solvay Chemicals.

The telomerization of glycerol has also been investigated as an atom-economical route to get unsaturated ethers of glycerol (Scheme 15). Such amphiphilic glycerol ethers can be used as surfactants or emulsifiers after hydrogenation. The degree of substitution is important for this multifunctional nucleophile, as the fully substituted tri-telomers are not interesting in light of the intended application as surfactant/emulsifier or as reactive dilutors or defoamers. Selectivity of the process to the mono-telomers and/or di-telomers is therefore essential from an industrial point of view. It has to be noted, however, that while obtaining the individual pure compounds is of course desirable, a product mixture obtained from a telomerization process can actually also have the desired properties [86]. Especially in the case of substrates with many more or less chemically equal functional groups, mixtures of isomers will almost inevitably be obtained. The physicochemical properties of these mixtures can nonetheless be reproducible and tuned in highly bespoke ways, if consistent degrees of substitution can be achieved from run to run. This holds for substrates such as glycerol, but even more so for the mono- and polysaccharides that will be discussed in Sect. 4.2.

Behr et al. first reported on the Pd/TPPTS-catalyzed telomerization of glycerol, using a biphasic system in which glycerol, water and liquefied butadiene are mixed intensively [83]. This biphasic system was chosen in order to address issues concerning mono-telomer selectivity as well as efficient catalyst recycling. Indeed, the limited solubility of the desired mono-telomer product in water leads to high selectivity for this compound as further conversion to di- or tri-telomers in the water phase is prevented. A downside of the system is that moderate activities are observed due to mass transport limitations. At a 1,3-butadiene/glycerol ratio of 2.5, with 0.06 mol% $Pd(acac)_2$ (relative to glycerol) and a P/Pd ratio of 5, the mono-telomers were obtained after 4 h at 80°C in a yield of 41% (first run) with a selectivity of >95%. Catalyst activity decreases after a number of runs, which is attributed to catalyst decomposition partly caused by oxidation of the TPPTS ligand. Leaching of palladium into the organic phase was not considered to be the cause of the observed deactivation. An additional study by the same group puts an emphasis on the use of additives to increase activity and selectivity and reduce leaching of the catalyst into the product phase to enable efficient catalyst recycling [87]. Addition of 2-methyl-2-butanol as a co-solvent decreased catalyst leaching while maintaining activity, whereas addition of cyclodextrins also gave a limited increase in conversion with similar or slightly decreased catalyst leaching. Addition of salts, acids or bases was all detrimental to activity and increased catalyst leaching. Notably, phosphonium salts, which act as ligand reservoir (see Sect. 3), allowed the catalyst activity to be kept constant for more than 230 h by reducing the amount of palladium that precipitates during reaction. In addition, 4-*tert*-butylcatechol (0.01 mol% of 1,3-butadiene) was shown to inhibit 1,3-butadiene polymerization, while retaining catalyst activity. The latter reaction is always a concern, as butadiene polymerization can lead to reactor fouling. Behr et al. have further developed this system into a continuous reactive extraction process on a mini-plant scale which allowed them to explore the influence of long reaction times on activity and selectivity. Reactions were run continuously for up to 250 h with a product stream of 10 g h^{-1}, under which conditions Pd leaching was limited to 20 ppm even at a phase separation temperature of 90°C. Continuous addition of TPPTS, phosphonium salt and polymerization inhibitor (4-*t*-butylcatechol) was essential for a constant product quality in runs of more than 100 h (Fig. 8) [64]. Catalyst deactivation gradually occurs if TPPTS and its phosphonium salt are only added at the beginning of the reaction, leading to reduction in telomer formation and a concomitant increase in butadiene dimer formation.

Bigot et al. also used biphasic aqueous conditions for their telomerization reactions of glycerol, focusing mainly on optimization of various parameters for not only mono-, but also di- and tri-telomer production [88]. Unlike Behr, a positive influence of the base sodium hydroxide on activity was observed under their

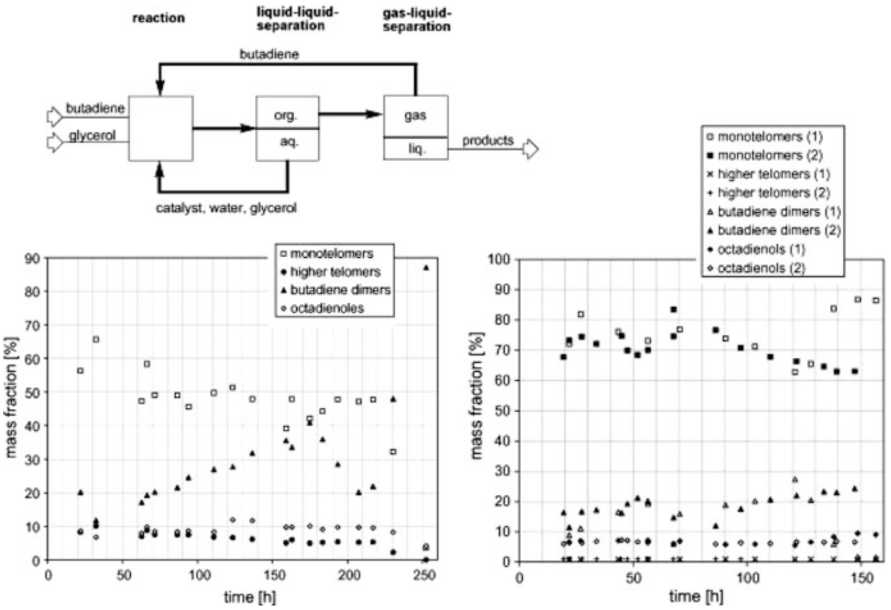


Fig. 8 Product quality with one-time addition (*left*) and continuous addition (*right*) of a phosphonium salt and polymerization inhibitor in a continuous reactive extraction set-up for the telomerization of glycerol. Adapted with permission from [64]

conditions (24% conversion after 2.5 h without base, 86% conversion in 1 M NaOH), with TOFs of up to 2,000 h^{-1}. Weaker bases such as Cs_2CO_3 or Et_3N were found to be less effective. The telomerization reactions were also performed under semi-batch conditions using gaseous rather than liquid 1,3-butadiene and an adjusted low or high water content. Although the reaction was considerably slower, this approach did allow for the determination of a reaction profile. An initial induction period was observed in which glycerol was converted, but telomers were not yet formed. This was attributed to the reduction of the palladium(II) source to palladium(0) essential for telomerization to occur. The influence of the amount of water added was also highlighted as quite different concentration profiles were obtained with low and high water content (Fig. 9). With little water present, there was a sharp maximum for the production of the mono-telomer, after which the mono-telomer was rapidly consumed to form higher telomers. On the other hand, when more water was added, the mono-telomer concentration went to a similar maximum of 52%, but only very slowly decreased afterwards as the formation of the higher telomers was considerably impeded. This points at the importance of the relative composition of the mixture and the phase behavior of the different components.

Palkovits et al. took a different approach to the telomerization of 1,3-butadiene with glycerol, screening various phosphine ligands and running the reaction without solvent. The importance of the steric and electronic properties of the phosphine ligand on activity and selectivity of the palladium catalyst has been highlighted in

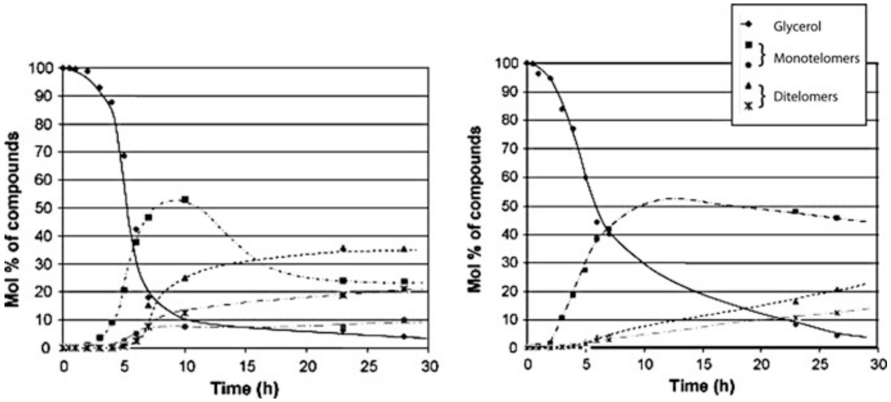


Fig. 9 Influence of water concentration on the concentration profiles of substrate and products in the telomerization of glycerol. Adapted with permission from [88]

the section on the mechanistic aspects of the telomerization reaction. From a screening of eight different phosphine ligands, the combination of palladium with the ligand TOMPP emerged as the most active catalyst system (Fig. 10) [32]. The TOMPP ligand seems to present an optimum between increased electron density on the phosphorous by the introduction of electron-donating *o*-methoxy substituents and increasing steric hindrance, as further substitution of the ligand with *o*-methoxy groups leads to a drop in activity. The Pd/TOMPP catalyst is highly active with a TOF of 5,182 h^{-1} obtained at 80°C at a butadiene/glycerol ratio of 4:1. The yield and selectivity was found to strongly depend on this ratio, ranging from 48% (ratio of 1:1) to 92% (ratio of 4:1) yield of glycerol ethers and selectivities of 70% (1:1) to 39% (4:1) for the mono-telomer. In all cases, significant amounts of tri-telomer were obtained, though, under the neat conditions applied (10–16%). This was attributed to the considerable solubility of the catalyst in the product phase.

Quite remarkably, the catalyst system was able to convert crude glycerol as well. The glycerol produced as by-product in biodiesel production is of rather low quality and its use in the common fields of application of glycerol is avoided. Refining via filtration, chemical treatment and fractional distillation is possible and done by larger biodiesel producers, but also rather expensive. New outlets have to be found therefore that can utilize this crude feedstock of the C3 building block and directly convert it into more valuable chemicals. The difficulty with crude glycerol is that it contains water, ash, methanol and fatty acid salts (soap), metal ions and other impurities from the transesterification process. Palkovits et al. could nonetheless convert crude glycerol directly with the Pd/TOMPP catalyst system. At a Bu/crude glycerol ratio of 4, a telomer yield of 73% was obtained. The selectivity pattern did change quite considerably: mono-telomer selectivity dropped to 20% and tri-telomers now constituted the major component (56%). This difference in product distribution was attributed to the longer reaction time needed for complete butadiene conversion (1.5 h instead of 0.5 h). The product composition after 0.5 h indeed

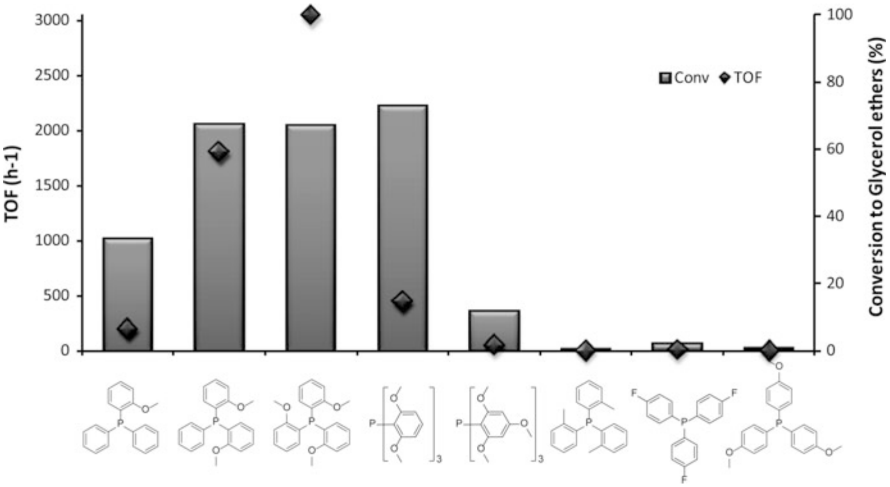


Fig. 10 Activity of different phosphine ligands in the palladium-catalyzed telomerization of glycerol. The tris(*o*-methoxyphenyl)phosphine gives the best results in terms of conversion and activity [32]

showed a product distribution similar to the one obtained with pure glycerol. Due to the large amount of water present, octadienol now appeared as a major by-product. It is nonetheless remarkable that the catalyst system can rather efficiently convert such a demanding crude substrate.

The same group later reported a more extensive study on the Pd/TOMPP system in which the effect of the metal precursor, addition of base, butadiene/glycerol ratio as well as the ligand/metal ratio were investigated [33]. Commonly used palladium sources such as Pd(acac)$_2$ and Pd(OAc)$_2$ both worked equally well; the use of the palladium(0) complex Pd(dba)$_2$ resulted in a higher activity, illustrating the fact that the catalytic cycle starts with a Pd(0) species and the requirement for the Pd(II) salts to be reduced before they can enter the cycle. Addition of triethylamine as base did increase the rate of reaction at lower butadiene/glycerol ratios, but activity dropped at a ratio of 4:1. The catalytic activity was found to be same at a ligand/metal ratio of 2 or higher, with excess of ligand required for the prevention of palladium black formation and reduction to Pd(O) in case of the Pd(II) precursor. Although the Pd/TOMPP catalyst is highly active, the selectivity to the mono- and di-telomer products should be improved when surfactant applications are targeted. As discussed previously, Behr et al. achieve selectivities of up to 95% for the mono-telomer of glycerol by using the Pd/TPPTS combination in a biphasic aqueous system, albeit it with a somewhat lower activity (TOF 248 h^{-1}). This exceptional selectivity is attributed to the limited solubility of the catalyst in the less polar product/butadiene phase. Aiming at combining both the desirable properties of the Behr system (high selectivity) with the high activity of Pd/TOMPP, a sulfonated TOMPP analogue was tested under the same neat reaction conditions, indeed resulting in an increased selectivity to the mono-telomers of 93% and hardly any tri-telomer production (1%). Unfortunately, the activity dropped significantly, and a TOF of only 137 h^{-1} was obtained [33].

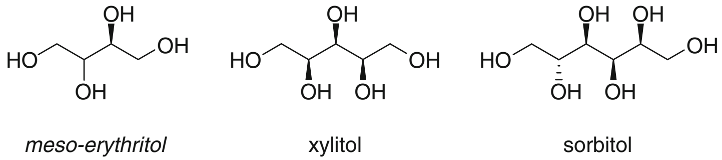


Fig. 11 Sugar alcohols erythritol, xylitol and sorbitol

Gordillo et al. used isoprene in the palladium-catalyzed telomerization of glycerol to make terpene derivatives that can be possibly used in the cosmetics and detergents sectors. A highly active palladium-carbene complex, as developed by Beller et al. [40], was chosen as the catalyst in order to convert this less reactive 1,3-diene. A combination of dioxane and polyethylene glycol was used as the solvent, the latter of which was telomerized itself as well, and good activities were obtained at 90°C, 5 eq. of isoprene to glycerol and addition of sodium *tert*-butoxide as base. No conversion occurred under neat conditions or with DMF as the solvent. A selectivity of >99% to the linear mono-telomer product was obtained, and only the tail-to-head and head-to-head isomers were formed (Fig. 1). Isoprene dimerization constituted an important side reaction with the ratio between dimerization/telomerization depending on the conditions employed. In contrast to the results obtained with phosphine ligands, the use of excess ligand resulted in a lower yield and the observation of an induction period.

4.1.4 Telomerization of Sugar-Derived Polyols: Sugar Alcohols and Dianhydrohexitols

The sugar alcohols, xylitol and sorbitol in particular are readily available platform molecules that can be obtained by hydrogenation of the corresponding C5 and C6 sugars. Hausoul et al. first reported in the open literature on the successful telomerization with the three sugar alcohols *meso*-erythritrol, xylitol and sorbitol using the Pd/TOMPP catalyst in *N*,*N*-dimethylacetamide (Fig. 11). In all cases, high butadiene (94 to >97%) and substrate conversions (80–93%) were observed in short reaction times (full conversion in less than 10 min). Average degrees of substitution of 1.8 are found if 3 eq. of butadiene is used. High TOFs of more than 11,000 h^{-1} are found, twice the value of the TOF observed for glycerol. Given the similar physicochemical properties of the sugar alcohols compared to glycerol, this sudden jump in activity is somewhat surprising. These sugar alcohols were all very reactive, consuming three 1,3-butadiene equivalents in 8 min at 80%, using a $Pd(acac)_2$ loading of 0.0234 mol% relative to the number of hydroxyl groups and a P/Pd ratio of 4. A French patent from 1994 also includes the telomerization of sugar alcohols sorbitol, xylitol, erythritol, maltitol and lactitol using a water-soluble phosphine under aqueous biphasic conditions [89].

Isosorbide, an 1,4:3,6-dianhydrohexitol, is readily obtained from the double dehydration of sorbitol. Amongst other chemical derivatives, diesters and diethers of sorbitol have already found application as solvents or plasticizers. Functionalization of the two alcohols groups attached to the rather rigid V-shaped framework of the two

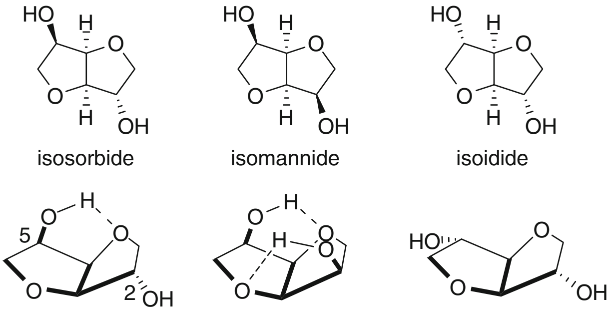


Fig. 12 The chemical structures of the anhydrohexitols isosorbide, isomannide and isoidide. The *bottom* structures show the two different orientations of the secondary alcohols

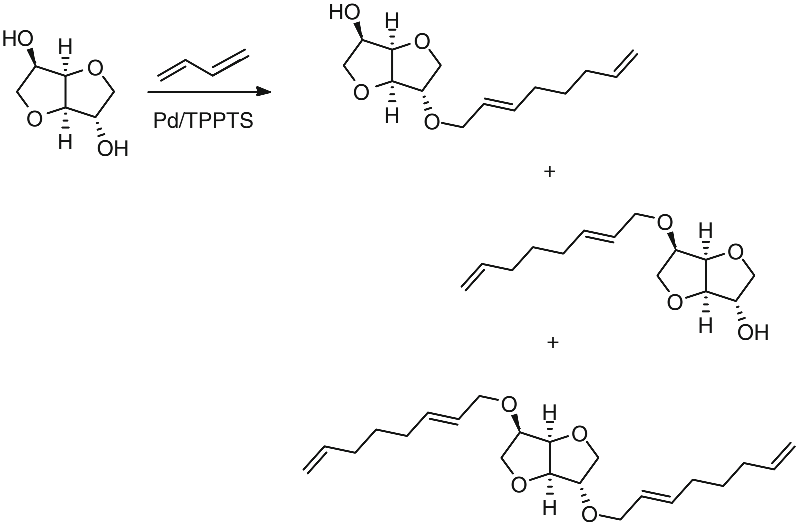
fused rings can lead to new applications of this renewable building block. Lai et al. [90] have studied the telomerization of isosorbide and its diastereoisomers isomannide and isoidide, which can be obtained from mannitol and iditol, respectively. The secondary alcohol groups are found in two different orientations in the three diastereoisomers (Fig. 12), which are expected to show different reactivity in the telomerization reaction.

The telomerization of butadiene was performed in molten isosorbide with 0.5 mL of a 0.5 M NaOH solution added to ensure the solubility of the TPPTS ligand and $Pd(OAc)_2$ as palladium precursor. Similar to the experiments performed by same group on glycerol (vide supra), butadiene was fed to the reaction continuously at atmospheric pressure. The two linear mono-telomers and the di-telomer were obtained as major products, with very little formation of the branched isomers (<3%) (Scheme 16).

Concentration profiles showed the mono-telomers to be the primary products, with the *exo*-2-hydroxy group being more reactive than the more shielded and hydrogen-bonded *endo*-5-hydroxy group. With continuous addition of butadiene, a final yield of 60% di-telomer was obtained after 24 h. If the reaction was run with 5 eq. of butadiene loaded in the reactor, but without base, mono-telomer selectivity was 97% after 2 h at 68% conversion. Addition of an NaOH solution resulted in complete conversion of isosorbide, accompanied by a large increase in di-telomer formation (up to 60%). Isomannide and isoidide gave almost exclusively the mono-telomer under aqueous biphasic conditions at more or less the same conversion levels (around 60%). Competitive reactions between isomannide and isoidide in DMSO and water showed improved reactivity of the *exo*-hydroxy group in aqueous media.

4.2 Telomerization with Mono- and Polysaccharides

The polysaccharides cellulose and hemicellulose are two major components of lignocellulosic biomass and form an abundant, non-edible and renewable source of carbohydrates. Other sources include starch, chitin, inulin and smaller



Scheme 16 Telomerization of butadiene with isosorbide

saccharides such as sucrose. The constituent monosaccharides, e.g. glucose for cellulose and starch and mainly various pentoses for hemicelluloses, will therefore be key building blocks in future biorefinery schemes. The carbohydrates do pose certain challenges to selective conversion, however, as the sugars are quite complex, polyfunctional and sensitive to acids, bases and heat [91]. Much effort has been invested in the selective conversion of sugars into complex target molecules of very high-value, to be used for various biological applications. In order to serve as viable building blocks in the biorefinery, new routes have to be developed that can allow the direct, facile functionalization for the production of value-added bulk chemicals as well. The telomerization reaction of butadiene with various carbohydrates has been quite extensively studied in this respect. A recent review by Bouquillon et al. focuses on the telomerization of butadiene with mono- and polysaccharides. This substrate category will therefore only be succinctly discussed here [22].

The alkyl glycosides that can be formed in this manner are suitable as nonionic surfactants; they also possess excellent biological compatibility, which makes them good candidates for use in mild detergents or as emulsifiers in cosmetics or food [92]. An important advantage of alkyl glycosides in terms of sustainability and green chemistry is their biodegradability, so their environmental impact is very limited. Selectivity in telomerization with sugars is again a key issue: ideally, the degree of substitution can be tuned so that alkyl glycosides with hydrophobicity tailored to their ultimate application can be produced. The synthesis of C8 glycosides via telomerization thus provides an attractive alternative to the well-known Fischer glycosidation.

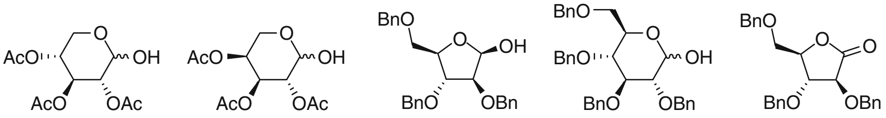


Fig. 13 From *left* to *right*: tri-*O*-acetylated D-xylopyranose, tri-*O*-acetylated L-arabinopyranose, *O*-benzylated D-arabinofuranose, glucopyranose and the lactone by-product

4.2.1 Telomerization with Protected Monosaccharides

One method to overcome selectivity issues during telomerization is to chemically protect all but one alcohol functionality. The first example of telomerization with a protected sugar was performed by Zakharkin et al., who successfully telomerized 1,3-butadiene with the primary alcohol of 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose [93].

Henin et al. first reported the telomerization of the anomeric hydroxyl group of protected pentose sugars [94]. Optimization of the linear/branched ratio, as the linear telomer is typically preferred for surfactant applications, was explored for the tri-*O*-acetylated pentapyranose sugars D-xylose and L-arabinose (Fig. 13) [94]. A screening of phosphine ligands and solvents revealed that using 2 mol% (relative to the sugar) Pd with 4 mol% of tris(*ortho*-tolyl)phosphine and a large excess of 15 eq. of 1,3-butadiene in THF gave an optimal l/b ratio of 15.6, with 87% yield after 8 h at 75°C. Excess of butadiene expectedly lowered the l/b ratio when triphenylphosphine was used, whereas higher sugar loadings had a similar effect. The latter was ascribed to enhanced coordination of the nucleophile to palladium to give an η^3-allyl palladium species with a phosphine ligand and the nucleophile coordinated. Such species of general nature [(η^3-allyl)Pd(P)(L)] are known to exhibit a lower intrinsic linear/branched ratio. The sterically less hindered β-anomer gave a higher selectivity to the linear isomer than the α-anomer, which is quite remarkable as attack at C1 is favored sterically, pointing at different reactivities for the two anomers.

Benzylated D-arabinofuranose and D-glucopyranose were also shown to be suitable nucleophiles, although long reaction times (24 h) were needed under the same conditions to obtain good yields. An important difference with the tri-*O*-acetylated pentose sugars is the formation of significant amounts of the lactone as an oxidized side product. The protected telomers could subsequently be hydrogenated and deprotected in one step over a 10% Pd/C catalyst at room temperature [95].

4.2.2 Telomerization with Unprotected Monosaccharides

The direct conversion of raw sugars without additional expensive and time-consuming protection/deprotection steps hold obvious advantages, but comes with considerable challenges regarding selectivity. Reactions are typically run in aqueous solution, using water-soluble phosphines such as TPPTS, but examples in organic solvents such as acetonitrile or DMF are also known.

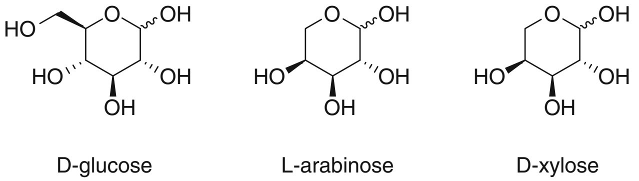


Fig. 14 The monosaccharides D-glucose, L-arabinose and D-xylose

Table 3 Selected results of the screening of ligand effects on conversions of L-arabinose and D-xylose and selectivity by Estrine et al. [99]

	Sugar	Ligand	Conversion (%)	Selectivity (%)		
				Mono-ethers	Diethers	Tri-ethers
1	D-Xylose	PPh3	97	69	28	3
2	L-Arabinose	P(*p*-tolyl)$_3$	97	54	39	7
3	L-Arabinose	P(*o*-tolyl)$_3$	86	69	25	6
4	L-Arabinose	P(*p*-MeOC$_6$H$_4$)$_3$	98	56	36	8
5	L-Arabinose	P(2,4,6-(MeO)$_3$C$_6$H$_2$)$_3$	6	84	12	4
6	D-Xylose	P(*n*Bu)$_3$ or P(*t*Bu)$_3$	< 2	100	0	0
7	D-Xylose	DPPE	8	100	0	0
8	D-Xylose	DPPP	71	87	13	0
9	D-Xylose	DPPB	8	100	0	0
10	D-Xylose	P(OEt)$_3$	8	88	12	0

Conditions: Pd(acac)$_2$ 4.4×10^{-5} mol; molar ratios sugar/Pd/P/butadiene/Et$_3$N = 150:1:2:900:150; 75°C; 45 min; 1 g of sugar in 5 mL DMF; *DPPE* diphenylphosphanylethane, *DPPP* diphenylphosphanylpropane, *DPPB* diphenylphosphanylbutane

The many different isomers that can be formed because of the multiple reactive sites of the nucleophile, the pyranose and furanose ring forms, and the different degrees of substitution often make analysis of the obtained product mixtures troublesome.

The telomerization of 1,3-butadiene with glucose was first reported in a patent awarded to Henkel and Zucker AG [96]. Using a Pd/PPh$_3$ system (0.07 mol% Pd relative to glucose; P/Pd = 2) in isopropanol/water, a glucose conversion of >90% was observed after 12 h at 85°C. Telomers with an average degree of substitution of 2 were obtained.

Telomerization with the unprotected aldopentoses L-arabinose, D-xylose and the aldohexose D-glucose (Fig. 14) in DMF was also extensively studied by the group of Henin [97–99]. Estrine et al. studied the influence of various parameters on L-arabinose and D-xylose telomerization, including the use of different amine bases and a large number of phosphine ligands, with the goal of determining conditions for the efficient conversion to mono-octadienyl ethers. The addition of an amine was beneficial for the reaction, but not essential as conversion was also observed without. Variation of the ligand led to conversions ranging from 2% to 99% with alkylphosphines and sterically hindered phosphines being less successful. The results of their ligand screening are shown in Table 3. The selectivity for the

Table 4 Composition of the bran syrup used for the butadiene telomerization

	%
Dry material	72.6
L-Arabinose	33.5
D-Xylose	54.2
D-Glucose	8.9
D-Galactose + D-mannose	1.7
Polysaccharides	1.2

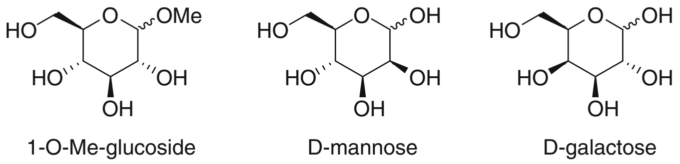


Fig. 15 1-*O*-methylglucoside, D-mannose and D-galactose

mono-octadienyl ether of D-xylose was 71% at 96% conversion, using triethylamine as additive and Pd/PPh_3 in DMF as the catalyst. The much lower reactivity of methyl xylopyranoside and the mono-octadienyl C1-ether compared to the free sugar further illustrates the higher reactivity of the anomeric hydroxyl group [98].

The same reaction was also studied in water using Pd/TPPTS, resulting in good selectivity towards the mono- and di-telomers [100]. The reaction proceeded somewhat more sluggishly in water, with the addition of a suitable amine such as $Et(iPr)_2N$ this time being an absolute requirement for activity. Again, the first etherification reaction involves the anomeric hydroxyl group. Sterically hindered amines such as $Et(iPr)_2N$ gave mainly the monooctadienylpentosides, whereas amphiphilic amines such as dimethyldodecylamine gave a mixture of di-telomers. The Pd/TPPTS catalyst could also be immobilized on KF/Al_2O_3, allowing conversion of the sugar up to 81% after 1 h at 80°C with a 77% yield of the mono-ether. The catalyst was recycled for five successive runs, although conversion dropped to 68% [101]. The various approaches taken for the synthesis of nonionic surfactants from D-xylose and L-arabinose, including telomerization, have been recently discussed by Bouquillon [102].

In another study, telomerization with bran syrup, primarily composed of L-arabinose, D-xylose and D-glucose was also successfully performed (Table 4) [103]. The crude telomer mixture showed similar surface activity as the purified compounds; therefore, the cheap crude mixtures may just as well be used in an industrial application of these alkyl glycosides.

Hausoul et al. [60] also reported on telomerization with aldopentoses (D-xylose, L-arabinose), aldohexoses (D-glucose, D-mannose, D-galactose), ketohexoses (D-fructose, L-sorbose) and the disaccharides D-sucrose and cellobiose, using Pd/TOMPP as catalyst without the addition of base in *N*,*N*-dimethylacetamide as the solvent (Fig. 15). The Pd/TOMPP combination had previously been shown to be highly active in the telomerization of various polyols (vide supra). Good conversion

Table 5 Results of the telomerization of 1,3-butadiene with various sugars using the Pd/TOMPP system [60]

Sugar	B/S[a]	Conversion[b] (%)	Yield[c] (%)	D.s.[d]	Time (min)	TON
D-Xylose	4.1	59	84	1.4	12	1,290
L-Arabinose	4.0	59	66	1.8	15	1,260
D-Glucose	4.2	82	87	1.9	25	1,390
1-*O*-Me-glucoside	4.0	95	86	2.3	25	2,080
D-Mannose	4.2	66	82	1.7	25	1,190
D-Galactose	3.9	71	64	2.2	25	1,190

Conditions: solvent *N*,*N*-dimethylacetamide; 0.0234 mol% (based on –OH) Pd(acac)$_2$, TOMPP, P/Pd ratio 4; 80°C

[a] 1,3-Butadiene/substrate ratio

[b] 1,3-Butadiene conversion

[c] Based on the sugar

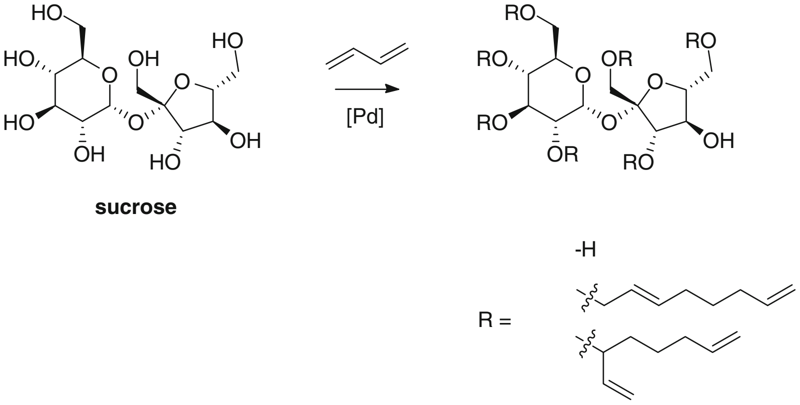
[d] Degree of substitution

(>80%) and high activity for a number of sugars was observed in short reaction times (<25 min) and low Pd loadings (0.0234 mol% –OH) as shown in Table 5. The degrees of substitution ranged from 1.4 to 3.3, establishing the reactivity trend: aldohexoses > aldopentoses > ketoses. Although good turnover numbers over 1,000 were achieved, the anomeric hydroxyl group was implicated in deactivation of the catalyst during the aldose and ketose conversions. This was exemplified by the results obtained with 1-*O*-methylglucoside and sucrose, acetals that both lack an anomeric hydroxyl group, for which no deactivation was observed.

4.2.3 Telomerization with Sucrose

Sucrose, or table sugar, is a disaccharide composed of glucose and fructose with the glycosidic bond made up of the reducing ends of both sugars. As a result, sucrose does not contain any anomeric hydroxyl groups, which are commonly associated with the catalyst deactivation that is observed with many of the reducing sugars. Telomerization with sucrose was first reported in a patent awarded to Henkel KGaA [104, 105]. Using a Pd/PPh$_3$ system (0.07 mol% Pd relative to sucrose; P/Pd = 2) in isopropanol, a sucrose conversion of >98% was observed after 12 h at 68°C in a semi-batch system with continuous addition of up to 13 eq. 1,3-butadiene at 2.5 atm. The average degree of substitution of the sucrose ethers was approximately 4.7–5.3 (Scheme 17). However, considerable amounts of octatriene and (isopropyl)-2,7-octadienylether were also observed.

Pennequin et al. [89, 106] observed a much-improved selectivity towards the mono- and di-telomers by using the TPPTS ligand in an aqueous phase with added isopropanol and NaOH. At a Pd loading of 0.40 mol% (relative to sucrose) with TPPTS (P/Pd = 3), a sucrose conversion of 73% was observed after 30 min, with a selectivity of 66% to the mono-telomer and 32% to the di-telomer. The group of Pinel also used Pd/TPPTS for the telomerization with sucrose in water, obtaining differently substituted sucrose telomers depending on the chosen reaction parameters [107].



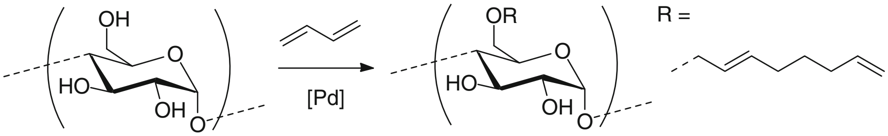
Scheme 17 Telomerization of 1,3-butadiene with sucrose

Using the Pd/TOMPP system, Hausoul et al. [60] reported a 95% yield of telomers after 14 min at 80°C, using *N*,*N*-dimethylacetamide as a solvent, 0.187 mol% Pd(acac)$_2$ (relative to sucrose), a P/Pd ratio of 4 and a 1,3-butadiene/sucrose ratio of 6. The telomers were found to have an average degree of substitution of 3.3. In contrast to other sugars tested under the same conditions, sucrose did not cause any apparent deactivation of the catalyst.

4.2.4 Telomerization with Starch

Starch is an abundant, inexpensive polysaccharide that is readily available from staple crops such as corn or maize and is thus is mostly important as food. Industrially, starch is also widely used in papermaking, the production of adhesives or as additives in plastics. For a number of these applications, it is desirable to chemically modify the starch to increase its hydrophobicity. Starch modification can thus prevent retrodegradation; improve gel texture, clarity and sheen; improve film formation and stabilize emulsions [108]. This may, for example, be achieved by partial acetylation, alkyl siliconation or esterification; however, these methods typically require environmentally unfriendly stoichiometric reagents and produce waste. Catalytic modification, such as the palladium-catalyzed telomerization (Scheme 18), of starch may provide a green atom-efficient way for creating chemically modified starches. The physicochemical properties of thus modified starches are discussed by Bouquillon et al. [22].

There are a number of unique challenges in telomerization with starch: for a suitable hydrophobicity, only a very low degree of substitution (<0.1) is required. While this means that lower catalyst activity can be acceptable, the catalyst must still be active at low 1,3-butadiene concentrations. In addition, starch may gelatinize at elevated temperatures, thus losing its desired properties. Furthermore, starch is practically insoluble in water at room temperature, making efficient interaction between the catalyst and starch difficult.



Scheme 18 Telomerization of 1,3-butadiene with starch

The group of Pinel developed a suitable catalyst system based on $Pd(OAc)_2$/TPPTS in a 1–5 solvent mixture of 0.1N NaOH with isopropanol [108]. Particular emphasis was put on controlling the degree of substitution, defined as the moles of substituted hydroxyl groups per anhydroglucosidic unit, i.e. with a theoretical maximum of 3. Based on the results with simple alcohols, the primary alcohol of the glucoside is expected to react first. The influence of time, reaction temperature, catalyst loading, solvent, etc., on the degree of substitution was studied. Although the system was highly active at 90°C, producing starch with a degree of substitution of 0.43 after 3 h, the starch was largely gelatinized at the end of the reaction. The reaction was also found to proceed at 50°C, allowing starch with a suitable degree of substitution of 0.06 to be obtained after 3 h, using only 0.012 mol% Pd relative to the number of –OH groups. A rather large excess of 1,3-butadiene (1.5 per –OH equivalent) was required for good reactivity at these low conversions with the modified starches not yet meeting the required specifications for industrial use, in particular the preservation of the granular aspect of starch [108].

Two major improvements were subsequently discovered: the addition of 12.5 wt% of sodium sulphate (Na_2SO_4) stabilizes the starch sufficiently to allow reaction at 50°C without degradation [109]. Dimethyl isosorbide was used as an unconventional green co-solvent. After optimization of the reaction parameters, high butadiene conversions (up to 93%) could be obtained, while maintaining the granular structure of starch. Secondly, the addition of a strong neutral or cationic surfactant, such as IGEPAL® CO-890 or cetyltrimethylammonium bromide (CTAB), greatly enhanced reactivity at low 1,3-butadiene concentrations and negated the need of isopropanol as co-solvent (Table 6) [110, 111]. The authors explain this effect by the formation of 1,3-butadiene-filled micelles, which are closely associated with the palladium catalyst, de facto creating a local high concentration of 1,3-butadiene. In addition, the basic conditions induce a partial negative charge on the starch, enhancing interaction between the starch and positively charged micelles (Fig. 16).

4.3 Telomerization with Phenols

The previous section illustrates that the polysaccharide components of lignocellulosic biomass provide ample opportunities for the telomerization reaction to convert (hemi-)cellulose-derived renewable building blocks such as saccharides, sugar alcohols and polyols into valuable bulk chemicals. The third key component of

Table 6 Influence of surfactant on the telomerization with starch at low 1,3-butadiene concentrations [110]

Surfactant	HLB[a]	D.s.[b]	Conversion (%)[c]
None	–	0.02	30[d]
SPAN® 20 (Neutral)	8–10	0.01	13
IGEPAL® CO-890 (Neutral)	16	0.08	100
CTAB (Cationic)	21	0.07	93

Conditions: 64 g starch, 3.2 g 1,3-butadiene, 100 mL H_2O, 8 g Na_2SO_4, 1.38 wt% NaOH, 5 mmol L^{-1} surfactant; [(π-allyl)Pd(TPPTS)$_2$] 0.4 mol% relative to 1,3-butadiene; 50°C, 6 h

[a] Hydrophilic/lipophilic balance of surfactant

[b] Degree of substitution calculated from 1,3-butadiene conversion

[c] Conversion of 1,3-butadiene

[d] After 24 h reaction time

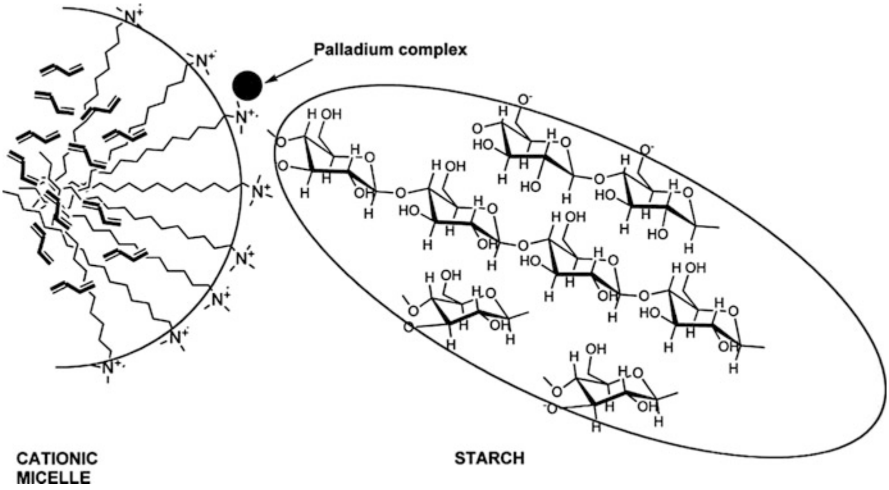


Fig. 16 Interactions between a micelle filled with 1,3-butadiene, the palladium catalyst and starch. Reproduced with permission from [111]

lignocellulosic biomass, i.e. the highly heterogeneous biopolymer lignin, is highly aromatic and can in the future serve as the primary source of renewable (functionalized) aromatics. While phenol is as of yet not readily available from renewable resources, many efforts are currently devoted to the catalytic valorization of lignin to valuable chemicals including phenolics [23]. The polymer lignin is built from the three lignin monomers *p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol, substituted phenols that are to different degrees methoxylated (Fig. 17). Depolymerization and partial deoxygenation could result in (methoxylated) phenolics, which are suitable substrates for telomerization reactions. Phenol is one of the envisioned products and can at the same time serve as a model compound for the expected degraded lignin stream [23]. The telomerization reactions with phenols are discussed below.

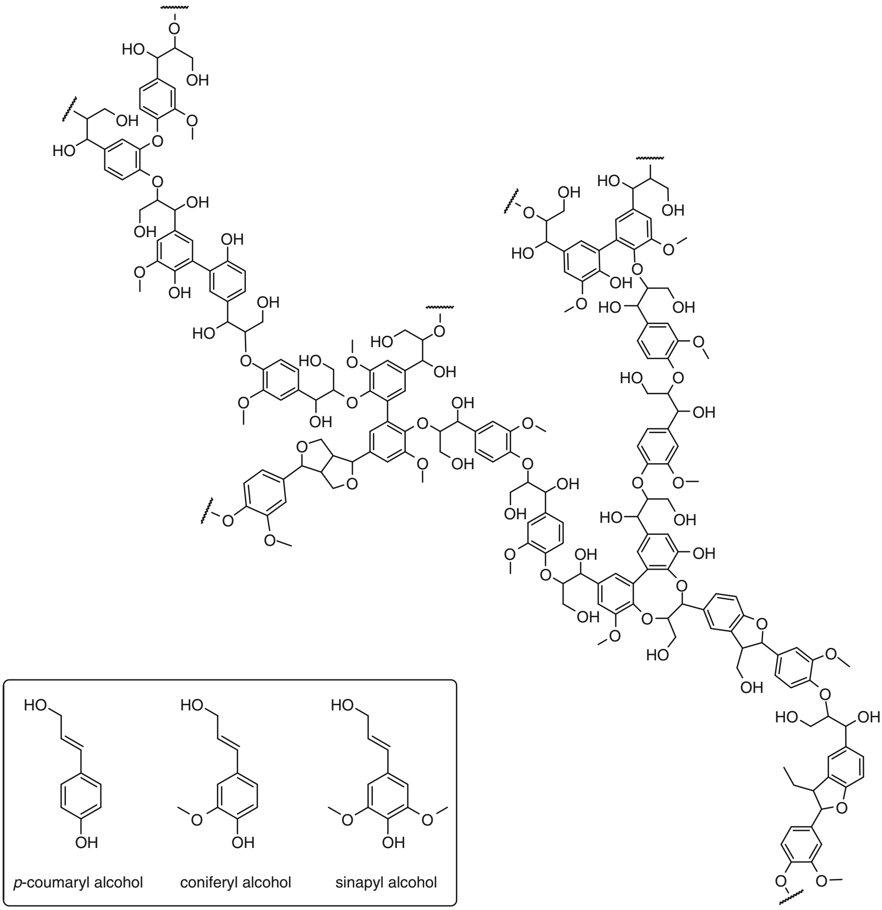


Fig. 17 Schematic representation of a softwood lignin structure, with the monolignols, the building blocks of lignin, depicted in the inset

The reaction of phenol with butadiene actually led to the initial discovery of the telomerization process by Smutny in 1967. Phenols with *p*-Cl, *p*-CH_3, *p*-OMe, 2,6-dimethyl and 2,4-dichloro substituents were also successfully converted. Isoprene could also be used to give the corresponding phenoxydecadienes [2]. Smutny also noted that the initially formed phenoxyoctadiene was almost fully converted to 1,3,7-octatriene (85% yield) if Pd/PPh_3 and sodium phenoxide were added to the reaction mixture before distillation at reduced pressure. Since this initial report, relatively little attention has been paid to phenolics as substrates in the telomerization reaction. This might be because the telomerization of phenol comes with additional challenges with regard to selectivity. Indeed, the regioselectivity in the telomerization of butadiene with phenol is often under thermodynamic control. This is in contrast to alcohols, such as methanol, and probably other alcohols as well, where the reaction is usually operated in the kinetic regime [46, 94]. It is important to realize this when one is particularly interested in

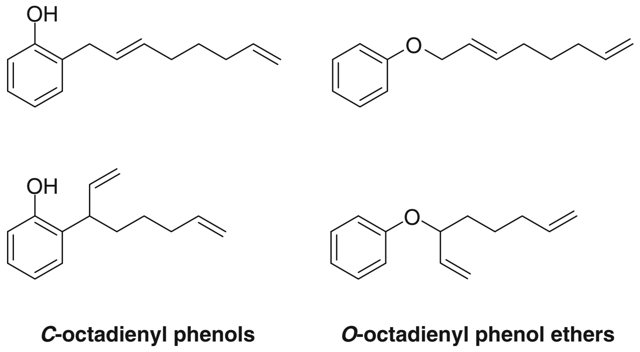


Fig. 18 The major products of the telomerization of 1,3-butadiene with phenol

obtaining optimal linear/branched ratios, as the energy difference between the linear and branched products is only small.

Furthermore, in addition to the *O*-octadienyl phenol ethers, ring-alkylated *C*-octadienyl phenols can also be obtained, in particular with electron-rich phenols (Fig. 18). Various routes can potentially lead to these ring alkylation products. *C*-alkylated products could, for instance, be obtained from the *O*-alkylated products by a subsequent Claisen rearrangement. Note that in this case, the branched *o*-octadienyl phenol product results from a Claisen rearrangement of the linear *O*-telomer and the linear *o*-octadienyl phenol from the branched *O*-telomer, reversing the linear/branched ratios. Cope rearrangement of the intermediates can subsequently give rise to *p*-alkylated octadienylphenols. However, the (thermal) Claisen rearrangement requires temperatures that are quite a bit higher than the temperatures at which the telomerization reactions of phenolics are usually run (<100°C). Alternatively, a palladium-catalyzed variation on the Claisen rearrangement could convert the *O*-alkylated products to *C*-alkylated ones. Kuntz et al. have shown this to occur for allyl ethers of phenol and guaiacol [112]. The group of Muzart studied the rearrangement of 1-phenoxy-2,7-octadiene itself in the presence of various metals [113]. The mechanism of the rearrangement would then entail the reversal of the product formation step, leading to an η^3-allyl species, followed by nucleophilic attack of the C2 and C4 carbons or the aromatic ring, leading to *ortho* and *para C*-alkylation, respectively. The nucleophilicity of C2 and C4, which makes phenol a multifunctional substrate, is caused by the ambident character of the phenolate anion, which is further increased by electron-donating substituents on the ring. The latter step will be slow, but does provide an irreversible thermodynamic sink. Both the ether as well as the alkylated phenol products can serve as the building blocks for various applications including insecticides or pheromones [114]. The *C*-alkylated products have the advantage that the phenol group is still available for further modification.

Weigert et al. used nickel catalysts with different phosphorous ligands with the aim of actually steering selectivity away from the telomer product, to obtain single butadiene addition products, phenoxybutenes. The linear and branched phenoxyoctadienes were often obtained as the major product, though [115]. Beger also used a nickel-phosphine catalyst to find a mixture of products, including the *O*-telomers of phenol [116]. Kaneda tested phenol with their polymer-bound palladium catalyst, showing fast conversion and good initial activity for the telomer products (95% after 2 h with a linear/branched ratio of around 3), with prolonged reaction times (18 h) resulting in an increase in octatriene formation. The authors also noted that the phenol telomers are more easily converted to octatriene in comparison to, e.g. alcohol telomers [74]. This can be attributed to the better leaving group ability of the phenolate anion. Note that only *O*-allylated products were reported in these studies. Jackstell et al. included phenol in their screening of the activity of monocarbene–palladium complexes with various alcohols, getting reasonable activities (i.e. compared to the exceptionally high activity obtained with methanol), with a high chemoselectivity to the *O*-allylated products (linear/branched ratio of 98:2) at 37% conversion. This linear/branched ratio observed is unexpectedly high for phenol, substituted phenols such as *o*-cresol, and 2,4,6-trimethylphenol more expectedly gave much lower linear/branched ratios of about 5:1 under the same conditions. A Pd/TPPTS complex immobilized onto a KF/Al_2O_3 support converted phenol in acetone solution with 2 eq. of butadiene. The reaction is rather sluggish, but good conversions were obtained after the first run with high selectivities to the linear telomer. No mention is made of *C*-allylated products [117].

The group of Beller showed that *C*-allylated products can be obtained selectively if naphthol or electron-rich phenols are used with butadiene or isoprene [118]. Reactivity could be steered to the C–C coupled product by using a Pd/PPh_3 ratio of 1:3 and addition of 1 mol% of Et_3N to give a C/O telomer ratio of $>50:1$. The high selectivity is attributed to the good leaving group ability of the naphthol group, meaning that the *O*-telomers are in equilibrium with the key η^3,η^2-intermediate. Formation of the *C*-allylated product results from the irreversible nucleophilic attack of C1, owing its nucleophilicity to the ambident character of naphthol. Accordingly, electron-rich phenols such as 3-methoxyphenol, 3,5-dimethoxyphenol, α-naphthol, 3-dimethylaminophenol and 3,4-methylenedioxyphenol could also be selectivity *C*-allylated. Phenol itself only gave *O*-allylated products under these conditions. The typical *O*-methoxy substitution patterns expected for lignin degradation products were not included in the substrate screening.

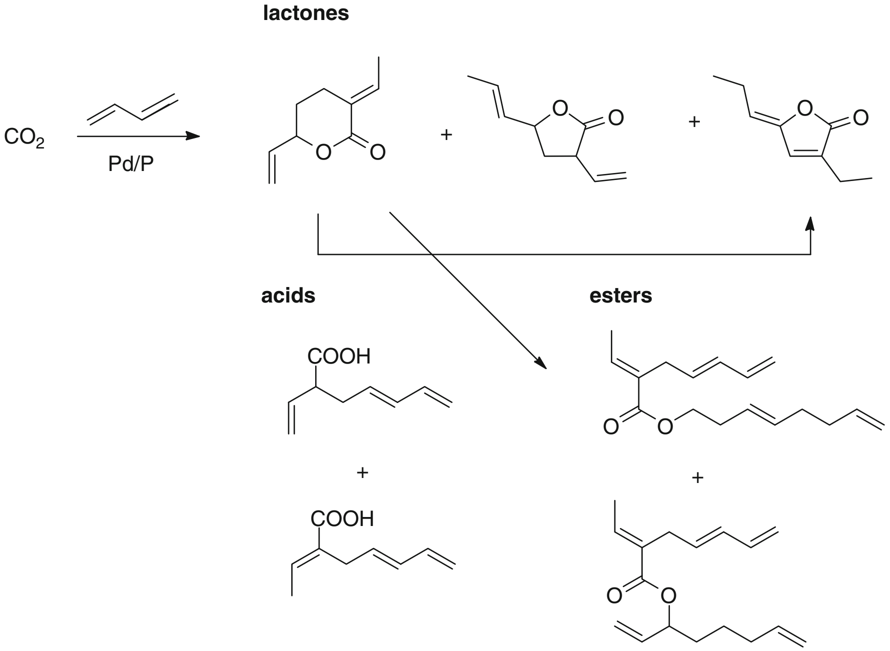
Behr et al. [114] investigated the selective formation of octadienyl phenol ethers in a liquid–liquid biphasic loop reactor. Although the Pd/TPPTS system showed good activity and selectivity (86% conversion with 74% selectivity towards the telomer after 5 h) in a lab-scale batch reactor, telomer yields in the loop reactor were insufficient for efficient phase separation. Telomerization with phenol was therefore deemed unsuitable for this type of reactor. The authors also noted that the *C*-allylated octadienyl phenol product rather than the telomerization product became the main product after 6 h of reaction, attributing this to a metal-catalyzed Claisen-type rearrangement.

4.4 Telomerization with Carbon Dioxide

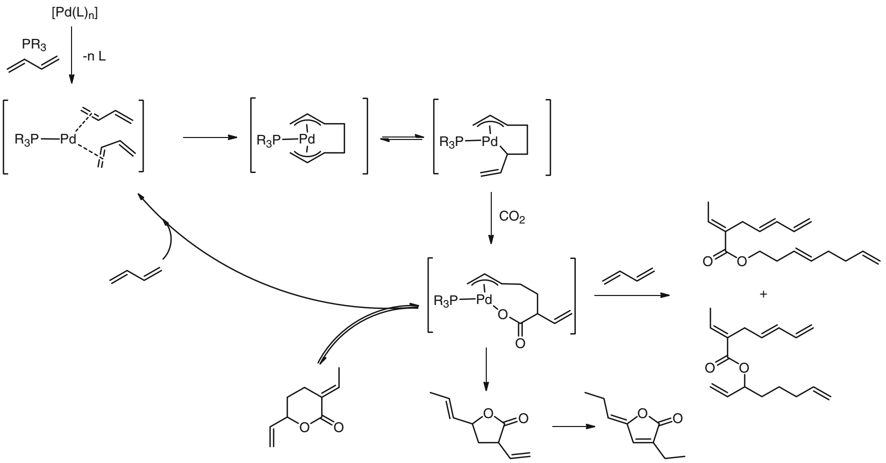
The direct utilization of carbon dioxide as renewable carbon source, as a complementary strategy to biomass valorization, holds great promise for the sustainable production of chemical and materials. Although abundantly available, its thermodynamic stability makes it difficult to use as a building block in the chemical industry. The telomerization reaction is one of the few examples in which carbon dioxide is readily converted into high-value chemicals. The telomerization of 1,3-butadiene with carbon dioxide can yield the five-membered ring lactones and the six-membered ring δ-lactone (*E*)-3-ethylidene-6-vinyltetrahydro-2*H*-pyran-2-one (Scheme 19). The latter lactone can be further converted into a wide range of different products, a topic that has been recently reviewed by Behr [24]. The telomerization with carbon dioxide was first reported by the groups of Inoue [119] and Musco [120]. Although lactones were successfully synthesized, yields of the δ-lactone were rather low (up to 14%) and by-products included octatriene, carboxylic acids and esters. The telomerization with CO_2 was subsequently studied in more detail by the groups of Behr [121] and Braunstein [122], with focus on the synthesis of the valuable δ-lactone.

The highly selective synthesis of the δ-lactone was accomplished by a Pd/phosphine catalyst with the use of a nitrile solvent such as acetonitrile proving essential. Highly basic trialkylphosphines, i.e. tricyclohexylphosphine in particular, selectively gave the desired lactone. The δ-lactone can be isomerized to the five-membered lactone using the same catalyst, but at higher concentrations. The latter lactone can also be directly obtained by increasing the catalyst concentration relative to the amount of butadiene used [121]. The δ-lactone could also be further reacted with butadiene to give the esters depicted in Scheme 19. A reaction mechanism was postulated that takes into account these observations, including the fact that highly basic phosphines work best (Scheme 20). Indeed, the equilibrium of the bis-allyl palladium intermediate is expected to shift to the η^1,η^3 species with more basic phosphines, facilitating the insertion of CO_2. The group of Behr has further optimized this reaction and developed the process to the mini-plant scale [123, 124]. Optimization studies revealed that the use of triphenylphosphine instead of tricyclohexylphosphine actually gave higher yields of the δ-lactone under the applied process conditions, albeit at significantly lower selectivities. Later work showed that the solvent acetonitrile could be replaced by more benign and environmentally friendly cyclic carbonates [125].

The reaction achieved considerable attention over the years, and various alterations have been reported. Behr also reported the combination of carbon dioxide, butadiene and ethylene oxide to give the hydroxyester of the acids depicted in Scheme 19. A nickel-catalyzed analogous system using triphenylphosphine or triisopropylphosphite takes a different route as cyclopentanecarboxylic acids are reported as the main product [126]. A palladium catalyst immobilized on a phosphine-decorated polystyrene polymer [127] or on silica also proved to be active [128].



Scheme 19 Telomerization of butadiene with carbon dioxide can give lactones, acids and esters



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Scheme 20 Reaction mechanism for the telomerization of butadiene with carbon dioxide proposed by Behr et al., adapted from [24]

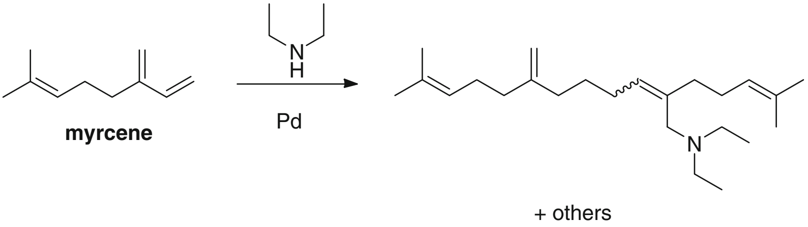
Pitter et al. built on the observation that nitrile solvents are beneficial for the carbon dioxide telomerization reaction and used hemilabile nitrile-tethered phosphine ligands. Butadiene conversions were in the range of 70–90%, and selectivities of up to 47% for the δ-lactone were reported. As a result of the appended nitrile, the reactions could now be run under neat conditions [129]. Dzhemilev et al. used a combination of both carbon dioxide and ammonia in the telomerization of butadiene to prepare *N*-substituted mono- and bis-octadienylformamides using $Pd(acac)_2/PPh_3$ (in 5:95 ratio at 55% yield) as catalyst and DMF as the solvent. Other products, such as dimethyloctadienylamine also formed, implicating a reaction with the solvent DMF [130].

5 Telomerization of a Renewable Taxogen: Myrcene

In all examples of the palladium-catalyzed telomerization discussed up till now, the nucleophile (telogen) can be considered renewable. The taxogens used (butadiene, isoprene), however, are still obtained from petrochemical resources, although butadiene could, in principle, also be obtained from renewable resources via the Lebedev process that converts (bio)-ethanol into 1,3-butadiene. Limited attention has been given in this respect to the great family of terpenes, as they provide direct access to renewable dienes for telomerization. In particular, those terpenes industrially available, which are derived mostly from turpentine, form an attractive group of substrates. Behr et al. recently used the renewable 1,3-diene myrcene in the telomerization with diethylamine, for instance [18]. The monoterpene myrcene is easily obtained from β-pinene, sourced from the crude resin of pines, by pyrolysis, and is currently already used in many different applications.

A yield of 69% of the tail-to-tail telomer (Scheme 21), the desired product, could be obtained using 0.05 mol% (relative to myrcene) $[Pd(MeCN)_4](BF_4)_2$ using PPh_3 as ligand (P/Pd ratio 8) in DMF, after 4 h at 100°C and a myrcene/diethylamine ratio of 2. The reaction was also studied in a thermomorphic solvent system, of which the components are immiscible at room temperature, but form one phase at the reaction temperature. This would allow easy phase separation and catalyst recycling. Although phase separation was difficult in methanol/octane due to the solubilising effect of unreacted diethylamine, the concept worked very well in DMF/heptane, with a very low catalyst leaching of 2 ppm Pd and P in the product phase (Table 7). The ability to recycle the catalyst was nonetheless not demonstrated.

Very recently, a heterogeneous palladium catalyst has been reported by Lopes et al. for the telomerization of myrcene with glycerol [19]. Supercritical carbon dioxide is used to overcome problems associated with the poor mutual solubility of the apolar diene and the polar oxygenate. Using a 5 wt% Pd/Al_2O_3 catalyst, low conversion of glycerol (9.8%) was achieved, but only mono-telomer products were formed. This high selectivity is attributed to the use of $scCO_2$, as the use of acetonitrile did yield di-telomer, albeit at twice the conversion level making a direct comparison difficult. Only tail-to-tail and tail-to-head telomers were reported with the products derived from the primary and secondary alcohol obtained in a



Scheme 21 Telomerization of myrcene. The linear tail-to-tail telomer drawn is the main product, although other telomers, hydroamination products and myrcene dimers may also be formed

Table 7 Results of the telomerization of myrcene in thermomorphic solvent systems

Solvent system			Yield (%)		Leaching (ppm)	
A	B	A/B[a]	33	Other[b]	Pd	P
MeOH	–	–	30	5	[c]	[c]
MeOH	Octane	50/50	42	13	[c]	[c]
MeOH	Octane	40/60	71	14	35	165
DMF	–	–	69	10	41	184
DMF	Heptane	60/40	81	10	1	2
DMF	Heptane	40/60	85	8	3	4
DMF	Heptane	30/70	67	6	13	57

Conditions: myrcene/diethylamine: 2/1, 0.5 MPa argon; $[Pd(MeCN)_4](BF_4)_2$ (0.05 mol%), PPh_3, P/Pd 8; 4 h, 100°C

[a] Molar ratio of solvents A and B

[b] Includes other telomers, hydroamination products and myrcene dimers

[c] No phase separation was observed

[d] Relative to myrcene

ratio of 2:1. The application of a heterogeneous catalyst with no additional ligands is quite surprising and warrants further investigation into the active species.

6 Concluding Remarks

Since its initial discovery in the 1967, the telomerization reaction has matured up to the point where it is part of two commercial processes. Much industrial and academic research over the past 45 years has been focused on improving the selectivity and activity of the catalyst with the industrially most relevant telogens water and methanol. The mechanistic insights, to which many research groups contributed, but Jolly and co-workers in particular, have greatly aided in our understanding of the catalytic cycle and thus allowed significant improvements in the more rational design of the catalyst and the process. In this light, the development of the *N*-heterocyclic carbenes as exceptionally active alternatives for the more traditional phosphine-based catalysts stands out. Given the way that the use of *N*-heterocyclic carbenes as ligands in catalysis has taken off in the last decade or so, more exciting developments can be expected in that direction. In addition to the elucidation of the mechanistic details and to catalyst development, much effort has been invested into addressing some of the more pressing problems associated with telomerization reactions, i.e. product selectivity and catalyst recovery and reuse. The various different approaches, in particular those explored by the group of Behr, have shown that for a number of different telomerization reactions, these challenges can in principle be addressed by choosing the proper process design. Indeed, this has been demonstrated by showing that scale-up of the processes from the lab bench to more industrially relevant proportions is actually feasible.

The flurry of activity in the field of the last years is mostly connected to the use of multifunctional substrates that can be sustainable sourced. The use of substrates, be it a multifunctional nucleophile or a green diene, thus provides a route towards valorization of the platform molecules to bulk chemicals that are at least partly renewable. The multifunctionality of many of the biomass-derived telogens provides considerable challenges with respect to controlling selectivity, but also ample opportunities for rapidly building up chemical complexity with a well-understood reaction. Indeed, the telomerization reaction provides a facile route to products which carry an unsaturated carbon skeleton appended to a chiral oxygenate and can be further converted to higher value synthons in numerous ways. The focus on bulk chemicals might have caused that the development of the telomerization reaction as a valuable tool in synthetic organic chemistry has been somewhat overlooked. Issues with regioselectivity, controlling the degree of substitution and the more general issue of catalyst activity will all need to be addressed for the multifunctional nucleophiles if new applications are to be realized. On the other hand, it should also be stressed that the fact that some substrates, e.g. the sugars or sugar alcohols, will almost inevitably give a mixture of products (if too elaborate protection/deprotection schemes are to be avoided) is not necessarily a disadvantage. Indeed, substrates, or even crude mixtures of substrates, that can be reliably and reproducibly converted into a mixture of products with a bespoke degree of functionalization can find application as such. The direct use of bran syrup, for instance, is a nice example of such an efficient and economical conversion of a crude feedstock to obtain the desired physicochemical properties, in this case for application as a surfactant.

Finally, the use of the expensive metal palladium as the metal of choice in the telomerization reaction holds obvious disadvantages for the economic feasibility of large-scale processes. Catalyst recovery and reuse should therefore receive further attention in future studies, for instance, by clever reactor design, or heterogenization of the catalyst. Alternatively, the use of palladium might be completely avoided if non-noble metals can be prompted to perform the same reactions when a suitably designed ligand environment is offered.

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Hydroformylation and Related Reactions of Renewable Resources

A. Behr and A.J. Vorholt

Abstract Today, the increasing global population and the rising consumption of fossil resources for energy and material use are important issues for research activities in the field of transformation of renewable resources. In petrochemistry, well-established reactions like hydroformylation are performed in multiton plants all over the world and are important examples for processing new resources beyond fossil feedstocks. This chapter deals with the application of three important reactions with carbon monoxide, specifically hydroformylation, hydroaminomethylation, and hydroesterification with renewables which have a C–C-double bond in the starting material. In these reactions, unsaturated oleocompounds and a variety of terpenes can be employed because of their naturally available double bonds.

Keywords Carbon monoxide • Hydroaminomethylation • Hydroesterification • Hydroformylation • Renewable resources

Contents

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1 Introduction

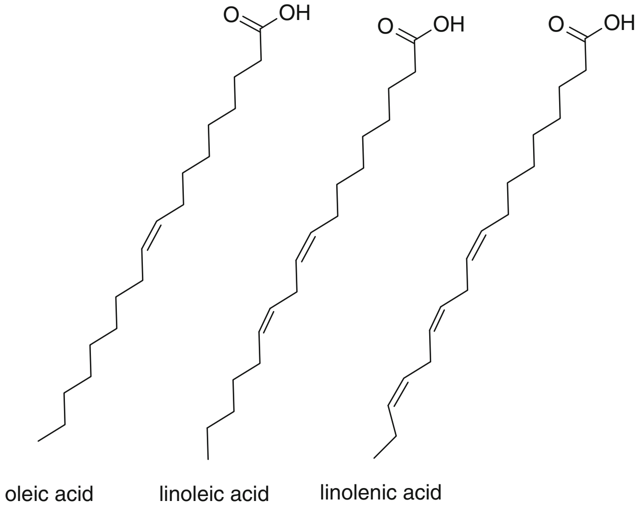
Natural products, with an annual biomass production of 170–180 billion tons, have a huge potential as resources for the chemical industry; so far, only 4% of these resources are used [1]. In Germany, about 16% of chemicals are currently produced from renewable resources. Today, mainly fossil resources such as coal, natural gas, and crude oil are used as starting materials in large-scale chemical processes. For the use of renewable raw materials, new ways have to be found to be able to use them effectively. There are basically three ways that are commonly used [2]:

- One way is to break the material down into C_1-blocks for further buildup chemistry to design classic intermediates.
- The second way is to synthesize chemical building blocks through chemical derivatization of renewables.
- The third is the direct use of the chemical structure of the renewable raw material.

Important groups of renewable raw materials are carbohydrates, lignin originating from wood, as well as fats and oils and various terpenes. They are available in large quantities and are already used for material and energy use. The high level of functionalization in comparison to petrochemicals often requires totally new techniques for their processing. In this regard, hydroformylation, hydroaminomethylation, and the hydroesterification of oleocompounds and terpenes are promising because of the C=C-double bonds they provide. The reactions of these two groups of renewables will be the main subject of this chapter. A short overview on the processing and the origin of these two resources will be given in the next section.

1.1 Fatty Compounds

For industrial applications, the group of fats and oils is one of the most important. Fats of vegetable and animal origin are used as food, feed, and for industrial proposes. At the beginning of the millennium, the ratio between food, feed, and industry use was 80:6:14. The increasing demand has increased the industrial use of oleocompounds, e.g., 54% of rapeseed oils were used in the year 2006 for industrial proposes. Worldwide, 144 million tons of fatty compounds were produced in 2008.



Scheme 1 Important unsaturated C_{18}-fatty acids

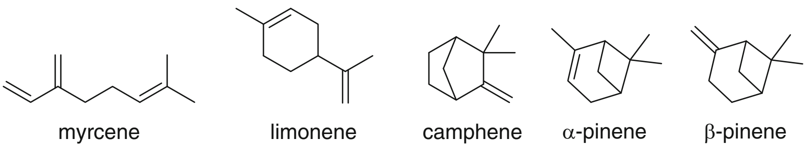
The most important fatty compounds are derived from soybean plants and palm oil. The main growing area of palm oil is Asia [3].

Fats and oils are triesters of the trivalent alcohol glycerol and three (different) even-numbered aliphatic carboxylic acids, the fatty acids. Fats and oils differ in the length and the number of unsaturated bonds in the carbon chain. The shorter C_{10}–C_{14}-fatty acids are obtained from coconut oil and palm kernel oil. These fatty acids are mostly saturated, and they are used in the manufacture of detergents. C_{18}-fatty acids are more widely used. Oleic acid, a C_{18}-fatty acid with an unsaturated bond on the ninth carbon atom, can be produced from many crops. Specific varieties or genetically modified plants, such as rape, have a content of over 90% oleic acid [4].

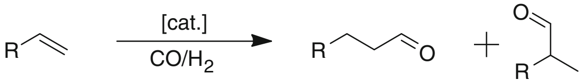
Unsaturated fatty acids or methyl esters are obtained via hydrolysis with water or by transesterification with methanol, while glycerol is produced as a by-product. The structures of some common unsaturated C_{18}-fatty acids, such as oleic, linoleic, and linolenic are shown in Scheme 1.

1.2 Terpenes

Terpenes are built out of C_5-isoprene units. There is a variety of terpenes ranging from C_5-terpenes which are called hemiterpenes to tetraterpenes with C_{40} atoms. There are also terpenes with more C_5-units, such as natural rubber, which is a polyterpene. Terpenes are also classified by the number of carbon cycles in the molecule, e.g., monoterpenes can have up to two cyclic systems in one molecule. Examples of some monoterpenes are shown in Scheme 2; myrcene is acyclic,



Scheme 2 Different types of monoterpenes



Scheme 3 Hydroformylation of a terminal olefin

limonene is a monocyclic monoterpene, whereas camphene and the pinenes are well-known bicyclic monoterpenes [5, 6].

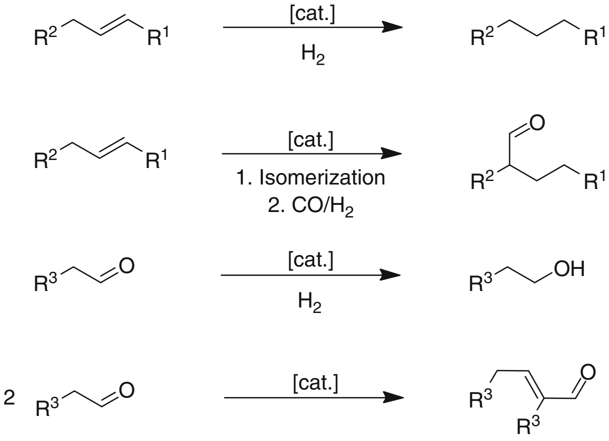
Terpenes are obtained either by processing wood in the kraft process in paper production or by collecting resins and turpentine from conifers. The scale of produced terpenoids in comparison with fats and oils is small. Applications for terpenes are in pure form as solvents, as odorous substances, or in dyes. Most terpenoids contain double bonds which are readily available to perform chemical reactions. A widespread component of turpentine is α-pinene, from which many fragrances are produced. A further often-used resource is myrcene, which is obtained by pyrolysis of β-pinene. Myrcene is an important base chemical to produce, for example, the fragrances nerol and geraniol [7].

2 Hydroformylation

Hydroformylation is a precious metal-catalyzed reaction of synthesis gas, a 1:1 mixture of hydrogen and carbon monoxide, and an olefinic organic compound to form aldehydes. The reaction was discovered by Otto Roelen in 1938 in experiments for the Fischer–Tropsch reaction [8]. In Scheme 3, hydroformylation of a terminal olefin is shown in which the addition of carbon monoxide can be conducted at both carbon atoms of the double bond, thus yielding linear (*n*) and branched (*iso*) aldehydes.

Due to Keulemans' rule, the addition of the formyl group is favored at the lower-substituted carbon atom. In the example of a terminal double bond, the linear regioisomer is preferred in comparison to the *iso*-isomer. In several applications, the linear products are more valuable than the branched products, so there are some efforts to influence the *n*:*iso* ratio [9].

In the presence of synthesis gas and a noble metal catalyst, other undesired reactions besides hydroformylation are possible and compete with hydroformylation. Hydrogenation and isomerization of the C=C-double bond, as well as



Scheme 4 Side reactions of hydroformylation

hydrogenation and aldol condensation of the generated aldehyde are common side reactions of hydroformylation (Scheme 4) [9].

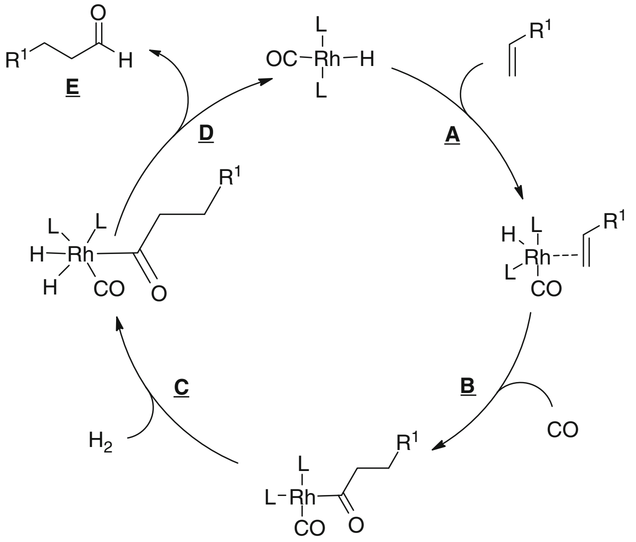
A common side product in hydroformylation is the hydrogenated starting material, e.g., an alkane. This hydrogenation can be influenced by choosing the catalyst species and by changing the partial pressure of hydrogen.

An interesting side reaction is the isomerization of the C=C-double bond in the molecule, which changes the regioselectivity of hydroformylation. Depending on the products, isomerization in this reaction is either suppressed or enhanced to use the isomerization. In the case of a terminal olefin and a desired linear product, isomerization is hindered for better selectivity for the *n*-aldehyde. In the case of internal double bonds and desired linear products, isomerization is used to bring the unsaturated site to the end of the molecule to conduct the reaction on the terminal end [10, 11].

Another side reaction is hydrogenation of the generated aldehydes to an alcohol. This reaction is used as an opportunity to obtain alcohols from olefins in one reaction step [12]. The literature shows also the condensation of aldehydes which are produced in the reaction. This reaction is used as a tool to form C–C bonds [13].

In hydroformylation, several metals have high catalytic activity. Roelen discovered hydroformylation by using cobalt as the catalyst metal. Cobalt catalysts need relatively harsh conditions with high pressures and temperatures. A more active catalyst metal is rhodium, which enables working under milder conditions. Other metals which can be employed in hydroformylation are ruthenium, palladium, iridium, or platinum–tin catalysts; however, only the most active rhodium and cobalt systems are industrially relevant. The development of hydroformylation catalysts in industry progressed through several steps.

The first-generation catalyst, a cobalt carbonyl ligand, was employed in the BASF process. In the next generation, phosphine species were added to milden the reaction conditions and to optimize the linear to branched ratio. In the third



Scheme 5 Mechanism of rhodium-catalyzed hydroformylation (formation of the *n*-aldehyde)

generation, rhodium phosphine catalysts were used for the first time, and the pressure could be reduced from 40–80 bar to 15–18 bar. In the Ruhrchemie/Rhône-Poulenc process, the fourth generation with a sulfonated triphenylphosphine ligand (TPPTS) was used for better recycling of the catalyst [9, 14]. The linear to branched ratio with this catalyst was higher than 95:5.

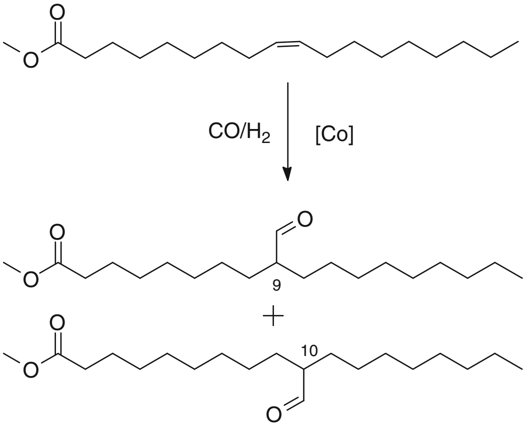
The mechanism of hydroformylation is well studied and is shown in Scheme 5 [15].

Based on $HRh(CO)_2(L)_2$, the mechanism is initiated by the coordination of an alkene molecule, resulting in a sixfold-coordinated complex (A). The following rearrangement to an alkyl rhodium complex happens before a carbon monoxide is added to the complex in the next step and inserted in the rhodium alkyl bond (B). The oxidative addition of hydrogen (C) and the release of the aldehyde by reductive elimination reform the starting rhodium complex (D).

2.1 Hydroformylation of Oleocompounds

The application of hydroformylation is not limited to unfunctionalized petrochemicals. Also, renewables are of interest for industrial applications. One good available resource is oleocompounds which possess C=C-double bonds [16]. Ucciani and Lai first investigated the hydroformylation of unsaturated fatty acid esters using cobalt catalysts such as cobalt laurate or dicobalt octacarbonyl (Scheme 6) [17, 18].

Scheme 6 Hydroformylation of methyl oleate



Frankel and coworkers also used $Co_2(CO)_8$ and demonstrated that, at 100°C, aldehydes are observed with a yield up to 84% [19]. The same conditions, but at 180°C, led to the corresponding alcohol because hydrogenation occurs as a consecutive reaction at the cobalt catalyst.

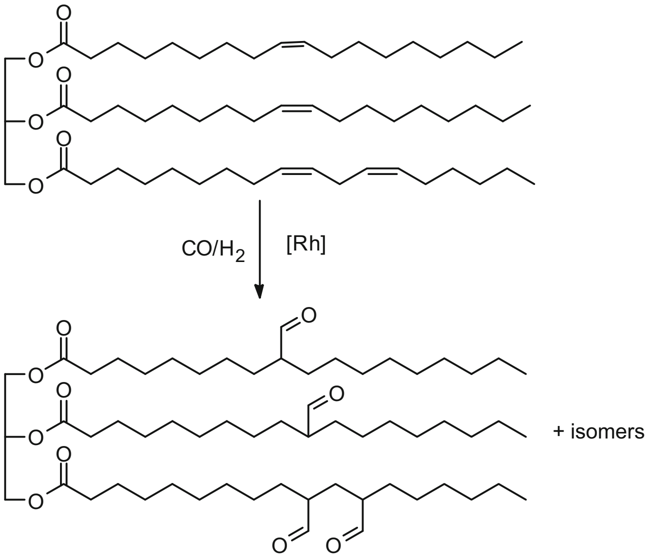
In the case of rhodium as a catalyst metal for the hydroformylation of methyl oleate, lower pressure and lower temperature have to be compared to cobalt catalysis [20, 21]. The use of rhodium is also advantageous because of the lower isomerization. Frankel showed that with a rhodium triphenylphosphine catalyst, hydroformylation occurs only on the ninth and tenth carbon atoms of the methyl oleate [22].

Also, bulky phosphite-modified rhodium catalysts are highly reactive for the hydroformylation of unsaturated fatty acid esters [23]. The catalyst was able to yield turnover numbers (TON) of 400–500 when moderate conditions with 20 bar synthesis gas pressure and 100°C were applied. These phosphites, like tris (2-*tert*-butyl-methyl) phosphite, have higher activity than phosphines like triphenylphosphine.

Triglycerides and technical-grade fatty acid esters can be used as the starting material in hydroformylation (Scheme 7). Soybean oil and technical-grade methyl oleate were hydroformylated by $[RhH(CO)_2PPh_3)]$ with triphenylphosphine as the ligand.

A quantitative conversion has been described within 4 h with 40 bar of pressure and at 100°C. The polyunsaturated fatty acids like linoleic acid were hydroformylated manifold. If $RhCl_3{\cdot}H_2O$ is employed, soybean oil cannot be hydroformylated because only the isomerization of conjugated fatty acids is obtained [24]. The direct processing of a fat without cleavage of the triglyceride is attractive for several applications.

Several oleocompounds were tested in hydroformylation with $Rh(CO)_2acac$ in toluene with triphenylphosphine. Soybean oil, high oleic sunflower oil, safflower oil, and linseed oil were employed at concentrations up to 6.53 mol L^{-1}. With



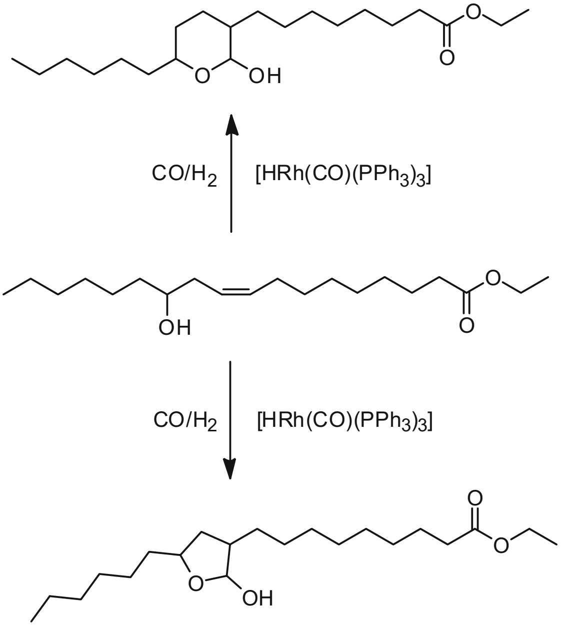
Scheme 7 Hydroformylation of a triglyceride with oleic and linoleic acids

linseed oil, this catalyst yielded a relatively high turnover frequency of 3,026 h^{-1}. Reduced activity of the catalyst was recorded in systems with polyunsaturated fatty acids because of the π-allyl complex with rhodium which is not catalytically active. The usage of phosphite in comparison to triphenylphosphine was less active in the hydroformylation of fatty compounds.

A kinetic study of the hydroformylation of soybean oil was undertaken by Kandanarachchi [25]; the pressure was varied between 40 and 110 bar, and the conversion rate increased with the pressure. The activation energy was calculated both for a rhodium system with $(PhO)_3P$ and with $(Ph)_3P$, showing that the phosphine species has a lower activation energy. Also, the temperature effect was studied, and it was found that the reaction rate increased until 100°C. Above that, the high temperature apparently inhibited the reaction due to phosphido-bridged clusters which are favored at higher temperatures.

Other C_{18}-fatty acids have also a high potential in hydroformylation, such as ricinoleic acid, which contains an additional hydroxy group at position 12 of the fatty carbon chain and which is not food relevant [26]. The hydroformylation of ethyl ricinoleate, derived from castor oil, shows selectivity for cyclization of the carbon chain because of the reaction of the hydroxyl group with the formyl group (Scheme 8).

Aldehydes have been observed as a by-product and can be obtained after protection of the hydroxyl group. It has been shown that cyclization to the furane or pyrane rings is not rhodium catalyzed [27].



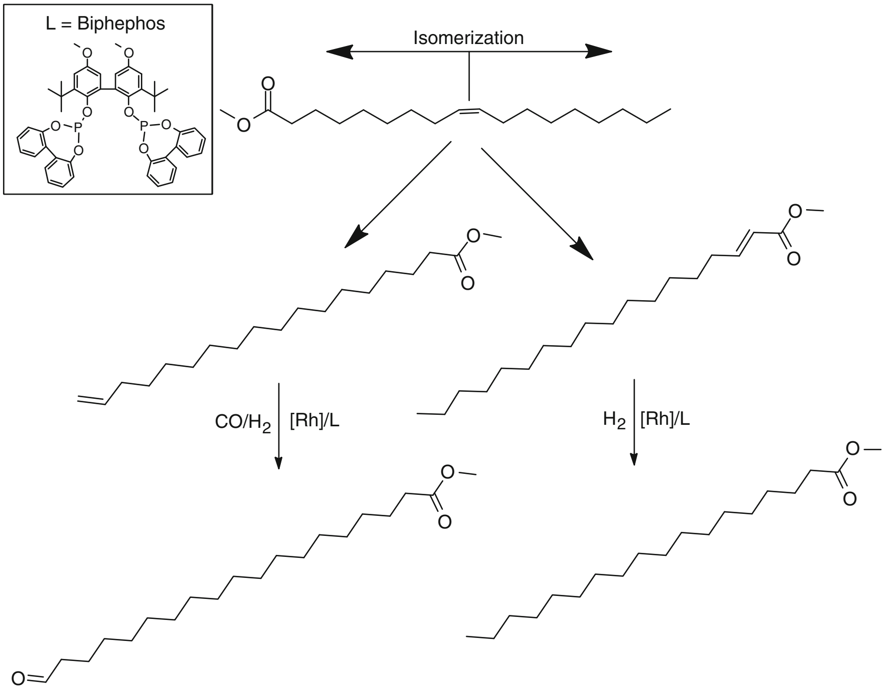
Scheme 8 Hydroformylation of ethyl ricinoleate

A very challenging task is the synthesis of α,ω-functionalized products from substrates with internal double bonds. In order to achieve linear aldehydes, isomerization of the internal double bonds at position 9,10–17,18 is necessary (Scheme 9).

The catalyst system [Rh(acac)$(CO)_2$]/biphephos shows high activity for isomerization with yields of 60% of branched isomers at 20 bar CO/H_2 pressure and 115°C [10]. With this catalyst system, a 26% selectivity of linear aldehyde from ethyl oleate was observed. The selectivity for the *n*-aldehyde was higher at 34% for linoleic acid. A hydrogenation side product was observed in the reaction due to the isomerization of the double bond toward the ester group, where hydrogenation is favored.

2.2 Recycling of the Noble Metal Catalyst

Friedrich et al. [28] describes a method of recycling a rhodium catalyst via thermal separation. The rhodium, which is fixed on a layer, is dissolved into the solution, in which triphenylphosphine stabilizes the rhodium. The reaction is carried out in a reactor with a synthesis gas pressure of 60 bar and at 120°C. After the reaction, the carrier is filtered before the product, methyl formylstearate, is separated by distillation. The rhodium-containing residue is united with the carrier before the organic

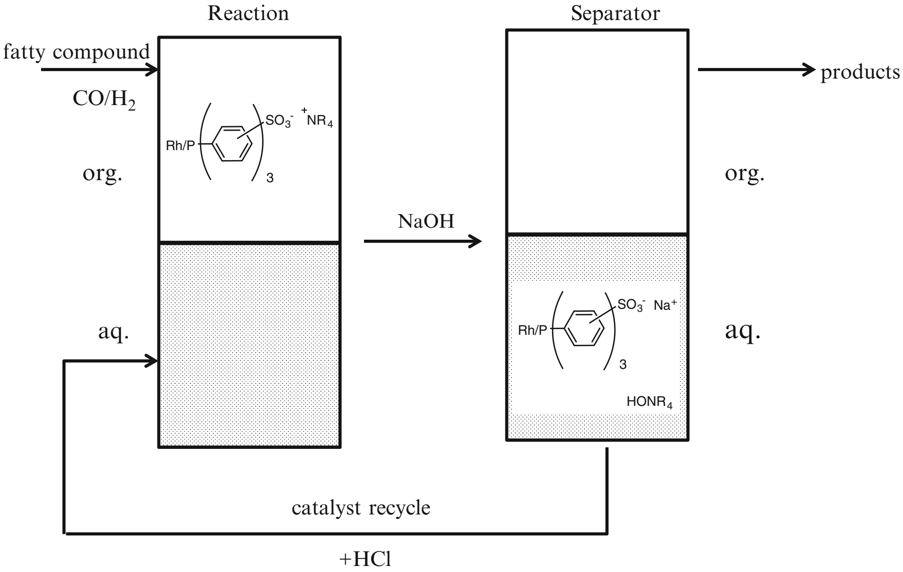


Scheme 9 Isomerizing hydroformylation

residue is burned to rebuild the original rhodium-containing carrier. The catalyst can be reused several times without any loss of catalyst reactivity.

Another possibility is separation by a liquid/liquid technique [29]. Bahrmann and Cornils showed recycling of a rhodium catalyst that was dissolved in an organic phase with aromatic phosphines which were sulfonated and contained 2–3 sulfonate groups. The sulfonate groups were coupled to ammonium groups with long carbon chains. This ligand ensured that the rhodium ligand complex was soluble in the organic phase during the reaction at 130°C and 270 bar. After the reaction, a caustic soda solution was added, the ammonium groups were split from the ligand, and the rhodium was separated to $<99\%$ in the water phase. The catalyst could be reused after treatment of the ammonium alkyl salts with acid to restore the ligand (Scheme 10).

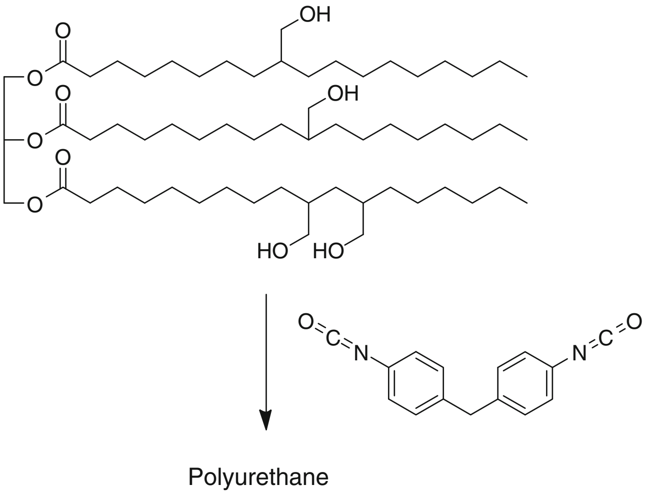
Fell et al. presented a micellar two-phase system in which fatty acid esters can be hydroformylated [30]. Short fatty acids react in a mixture of water and the substrate without adding any surfactants. The rhodium/NaTPPTS catalyst system was able to conduct the reaction of methyl 10-undecenoate at 100°C with 30-bar synthesis gas pressure with a conversion of 99% without any surfactant. The reaction of linolenic acid ester was hindered by phase transfer problems which could be overcome by employing surfactants. The addition decreased the reaction time, so the same rhodium catalyst could achieve a conversion for linolenic methyl ester of 100%. The authors



Scheme 10 Catalyst recycling in a liquid/liquid system

also describe the direct hydroformylation of linseed oil with high conversions in this micellar two-phase catalyst system. Tulchinsky and Abatjoglou developed various sulfonated ligands for a two-phase technique to recover precious metals in a hydroformylation process of fatty acids and esters [31–33]. A process for organic/water recycling of the catalyst was designed by the Dow Technologies; a detailed separation of the products from fatty acid esters is also described [34, 35]. Fell showed catalyst recycling for the hydroformylation of linolenic methyl esters: rhodium sulfate and triphenylphosphinemonosulfonate (TPPMS) were used as catalyst precursors and were dissolved in methanol at 200 bar and 120°C. Under these conditions, good conversion of the multiple unsaturated fatty acid compounds was described. For recycling, the methanol was distilled, and the catalyst was dispensed in water to separate the hydroformylation products. The water of the catalyst phase was evaporated before the catalyst was redissolved in methanol and the reaction could start again [36].

Fell also described the hydroformylation of fatty acids with heterogenized cobalt carbonyl and rhodium carbonyl catalysts [37]. The products of the reaction with polyunsaturated fatty acids were, depending on the catalyst metal, poly- or monoformyl products. The catalyst carrier was a silicate matrix with tertiary phosphine ligands and cobalt or rhodium carbonyl precursors on the surface. The cobalt catalyst was applied at 160–180°C and gave mostly monofunctionalized fatty acid chains. With linoleic acid mixtures, the corresponding rhodium catalyst gave mono- and diformyl derivatives. Therefore, the rhodium catalyst was more feasible for polyfunctionalized oleocompounds. The reaction was completed in a batch experiment over 10 h at 100 bar and 140°C; rhodium leaching was lower than 1 ppm.



Scheme 11 Polyurethane synthesis starting from an oleopolyol

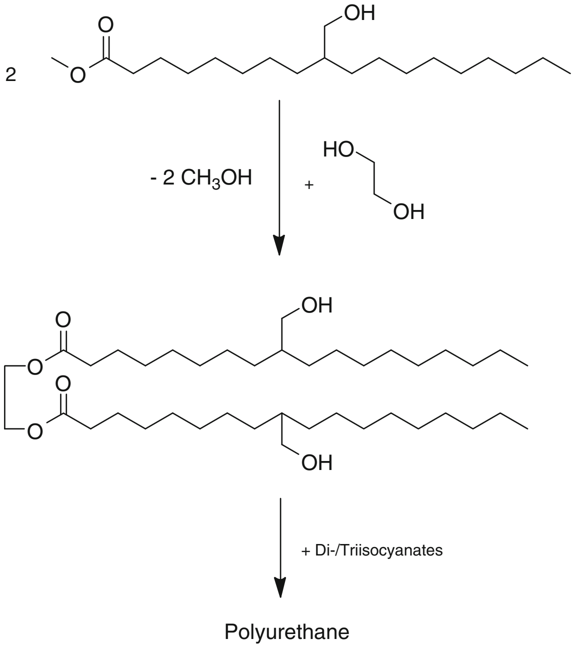
Another method for catalyst recycling was introduced by Davies and Hanson [38]. The heterogenization of the rhodium catalyst in an aqueous phase on a silica carrier enabled simple catalyst separation via filtration. Oleyl alcohol was hydroformylated in a thin aqueous phase on the catalyst surface at 50 bar and 100°C. Under these conditions, the yield was 97%, while the catalyst could be recycled several times without any loss of activity.

2.3 Applications

An important application for hydroformylated oils and fats is the production of polyurethanes. Hydroformylated fatty acids are hydrogenated to the corresponding diols and then converted to polyurethanes with diphenylmethane diisocyanate (Scheme 11). The polymer has a glass transition temperature of −33°C to −56°C, and the molecular weight is between 1,000 and 4,000 [12].

Dow also developed polyurethane foams from polyols via hydroformylation of fatty acids. The foams have properties which are comparable to foams from petrochemicals in terms of density and flexibility. The advantages of using sustainable feedstocks in viscoelastic foams are increased load bearings and tensile and tear properties [39, 40]. The hydroformylation and consecutive hydrogenation of fatty acids derived from seed oil can also be used to form low viscosity polyester polyols. Therefore, fatty acid methyl esters are transesterified with diols, e.g., glycol (Scheme 12). The polymer contains chemically active hydroxy groups which can be used for polyurethanes in coating applications [41].

Scheme 12 Polyurethane synthesis for coating applications

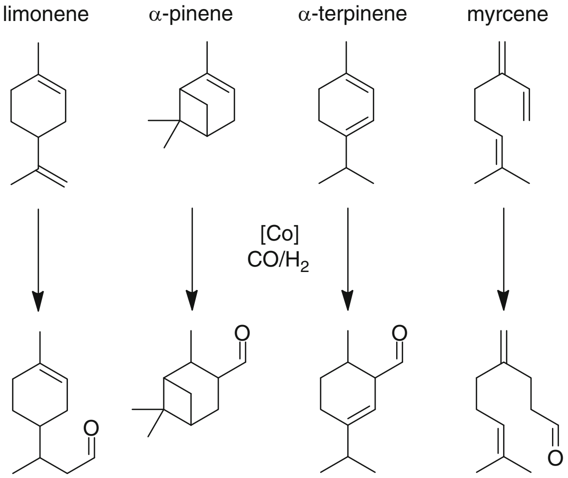


2.4 Hydroformylation of Terpenes

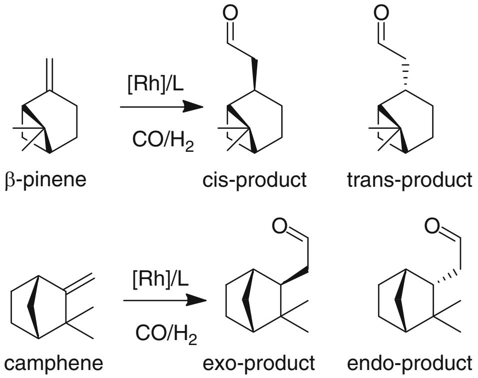
For centuries, monoterpenes have been widely used as odorants. Due to their molecular weight and their low boiling points, obtaining related odorant substances through derivatization is obvious. An effective method is the hydroformylation of limonene, α-pinene, α-terpinene, and myrcene. A comparison of the activity in hydroformylation of the four molecules was done in the 1960s using a cobalt catalyst with pressures of around 250 bar and a reaction temperature of 150°C (Scheme 13).

Myrcene and α-terpinene contain conjugated double bonds and are not as reactive as limonene and α-pinene. The product mixture is complex; besides the hydrogenated products and the alcohols, undefined high boiling point products also occur [42]. The two conjugated terpenes were also studied with rhodium phosphine catalysts. Within 7 h, 96% of α-terpinene reacts to aldehydes with high selectivity for the product shown in Scheme 13 [43].

A rhodium-catalyzed hydroformylation was also carried out with the bicyclic terpenes β-pinene and camphene [44, 45]. The influence of phosphine and phosphite ligands (L) on the formation of the different product isomers of the hydroformylation of β-pinene was studied by adding different mono- and bidentate ligands. However, the basicity of the ligands proved to be relevant for favoring the *cis*-isomer. A steric influence of the ligands to favor one isomer was not found (Scheme 14).



Scheme 13 Main products of the hydroformylation of some monoterpenes

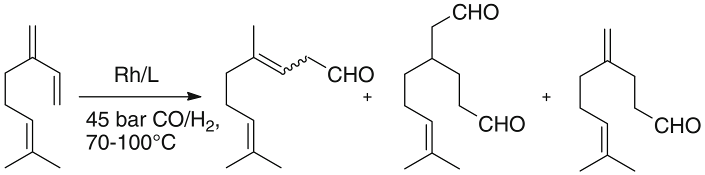


Scheme 14 Diastereomers of the hydroformylation of β-pinene and camphene

The addition of ligands in the hydroformylation of camphene influenced the reaction to *endo* product, while without ligands, an equal ratio between the *exo* and the *endo* product was observed. The selectivity for the two linear isomers was 100%.

Detailed investigations of myrcene in hydroformylation reactions were made by Gusevskaya [45]. The reaction led to nine products; the major products are shown in Scheme 15. Different precursors and ligands were studied in this reaction.

To control the reaction, different precursors and ligands have been employed to gain selectively for only one aldehyde. The terminal aldehyde was obtained with ligands with bite angles near 120° and a stiff backbone, e.g., xantphos. The aldehydes with an internal double bond were obtained with a monodentate ligand, e.g., triphenylphosphine, with a selectivity of 83%. Double hydroformylation was observed with higher pressures and temperatures.



Scheme 15 Main products from the hydroformylation of myrcene

An attempt at recycling the rhodium catalyst was made my Delmas [46]. An immobilized rhodium catalyst in a supported aqueous phase could convert limonene to 95% of the desired product. The selectivity for the linear product was 70%. A kinetic study showed that the reaction rate was first order.

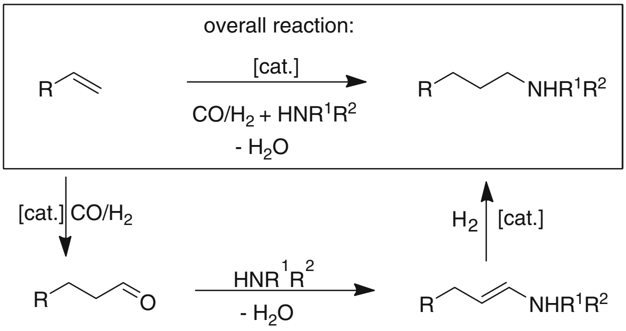
Another method for catalyst separation is the previously mentioned liquid/liquid technique which was studied by Gusevskaya with limonene, camphene, and myrcene in a toluene/biphasic system with Rh/TPPTS as the catalyst [47]. The addition of cationic cetyltrimethylammonium chloride (CTAC) was crucial to overcome the mass transport problems of this two-phase system. All three terpenes gave high conversions, between 71% and 96%, while the admixing of CTAC was positive in the case of myrcene and limone and negative for the reaction with camphene.

3 Hydroaminomethylation

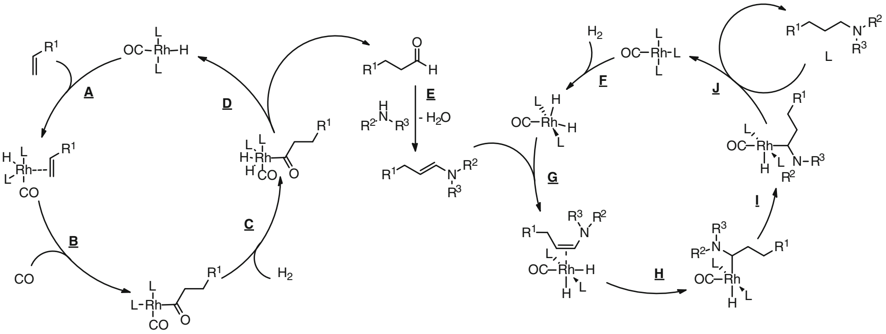
Hydroaminomethylation is a promising reaction to functionalize unsaturated compounds with an amino group [13, 48, 49]. The tandem reaction was discovered by Reppe in 1949 and has been further developed in recent years by Eilbracht and Beller. Hydroaminomethylation consists of three consecutive reactions which are carried out in the same reaction vessel [48]. The first reaction is hydroformylation which is followed by the condensation with an amine. Hydrogenation of the generated enamine/imine to the amine is the last step. The conditions for hydroaminomethylation are related to the hydroformylation reaction but are not similar due to the two other reactions. The reaction is called an “auto-tandem reaction” because two of the three reactions need the same catalyst [9] (Scheme 16).

This atom economic reaction, in which only water occurs as a by-product, is very attractive for forming various amines. Hydroaminomethylation includes three different mechanisms due to the three reactions involved. The mechanism of hydroaminomethylation is shown in Scheme 17. The first catalytic cycle is similar to hydroformylation, which is described above.

The aldehyde formed in the first cycle reacts with an amine (E) yielding an enamine. This coordinates to the rhodium dihydrido species (G) of the second catalytic cycle. The insertion of the enamine in the rhodium hydrogen bond (H) is the next step before the hydrogenated molecule is cleaved (J) and the active rhodium complex is restored by adding a hydrogen molecule (F).



Scheme 16 Auto-tandem hydroaminomethylation reaction of a terminal alkene (e.g., formation of the linear product)

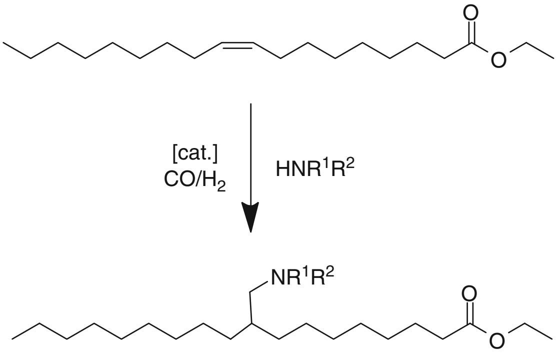


Scheme 17 Mechanism of hydroaminomethylation

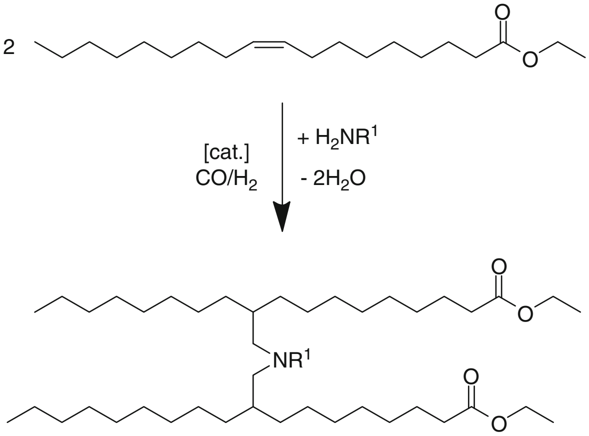
3.1 *Hydroaminomethylation of Oleocompounds*

In 2000, Behr and Eilbracht described the auto-tandem reaction of methyl oleate with various primary and secondary amines (Scheme 18) [50].

A rhodium catalyst $[Rh(cod)Cl]_2$ was applied at 140°C and 100 bar to achieve a yield of 99% in hydroaminomethylation of ethyl oleate and morpholine. Several amines were tested in the reaction with fatty compounds; hexylamine, benzylamine, aspartic diethyl acid, valinol, and diisopropylamine are further amines which can be employed in hydroaminomethylation. The conversion with primary amines showed that hydroaminomethylation can proceed twice on the amine. The dimer fatty acid ester bridged with an amine is a highly functionalized molecule with various applications. An excess of the primary amine during the reaction prohibits the reaction of the hydroformylation product with a secondary amine which is the product of hydroaminomethylation with the primary amine (Scheme 19).



Scheme 18 Hydroaminomethylation of ethyl oleate

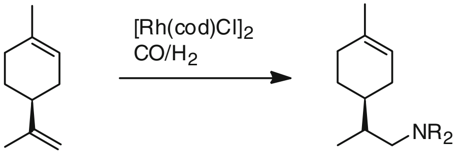


Scheme 19 Hydroaminomethylation of ethyl oleate with a primary amine

3.2 *Hydroaminomethylation of Terpenes*

Limonene is used as a starting material for growth regulators of tobacco plants. Hydroaminomethylation is able to reduce the number of reactions steps for their production to one. The reaction takes place with yields up to 93% after 20 h with a rhodium dimer as a catalyst (Scheme 20).

The second double bond is not hydroaminomethylated because of the mild conditions at 80°C and 80 bar and due to steric hindrance [51]. Graebin describes seven different products of the hydroaminomethylation of limonene [52]. The reaction time was reduced to 10 h by optimization of the catalyst including stepwise hydroformylation for 5 h and hydrogenation with pure hydrogen gas for 5 h. Isomerization was reduced by adding triphenylphosphine as ligand.



Scheme 20 Hydroaminomethylation of limonene

4 Hydroesterification

Hydroesterification is one of the “Reppe reactions” in which carbon monoxide, an alcohol, and an alkene react to esters (Scheme 21). This reaction is also called alkoxycarbonylation, hydroalkoxycarbonylation, and hydrocarbalkoxylation.

The reaction is precious metal catalyzed and was first described with nickel as the catalyst metal. Further development showed that several metals are active in this reaction; palladium is the most active catalyst metal and is widely used. In some cases, a Brønsted acid is added to stabilize the active catalyst. The regioselectivity of the reaction can be controlled by the addition of bulky chelating ligands. The employment of monodentate ligands, metallocenes [53–55], or other bidentate ligands [56–58] increases the ratio of linearity of the ester products.

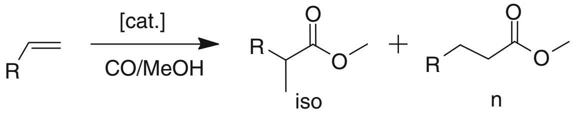
There are two mechanisms that have been proposed for hydroesterification: the hydride mechanism and the alkoxy mechanism. Here, the alkoxy mechanism will be shown in detail (Scheme 22).

The cycle is started with the formation of a Pd-alkoxy complex that reacts with CO to an alkoxycarbonyl intermediate. In the next step, the approach of the olefin and insertion into the carbonyl palladium bond is predicted. In the last step, the starting complex is rebuilt by the addition of an alcohol and the cleavage of the hydroesterification product [59].

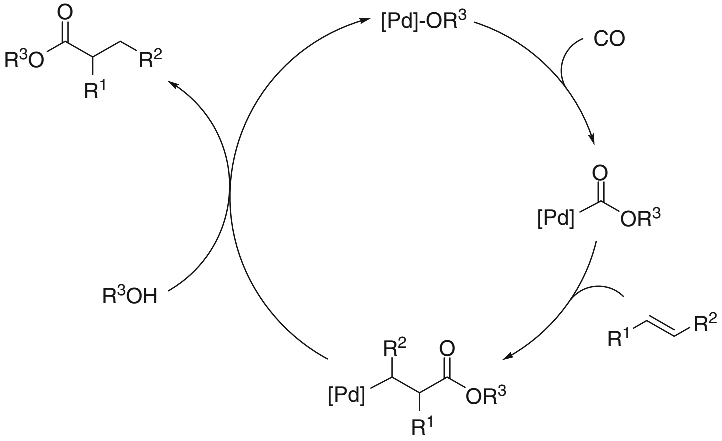
Hydroesterification is not a well-established industrial process yet. Several esters or carboxylic acids are made by a multistep synthesis with hydroformylation followed by an oxidation step and, if needed, a further esterification step. The lower economic importance of hydroesterification compared to hydroformylation is due to four causes, as determined by Kiss [59]:

- In hydroformylation, a high selectivity for the frequently desired linear products can be reached with the simplest phosphines.
- Hydroformylation is a well-established process in the chemical industry.
- Hydroesterification requires pure carbon monoxide gas.
- Hydroesterification with acid is a corrosive process.

In view of the technical implementation of hydroesterification of oleic acid methyl esters, these disadvantages have to be avoided.



Scheme 21 General reaction equation of hydroesterification



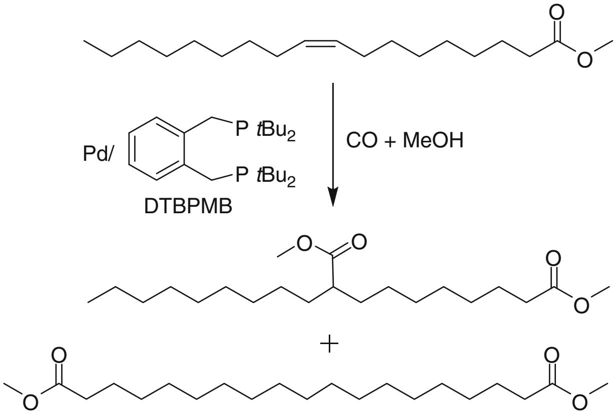
Scheme 22 Alkoxy mechanism of hydroesterification

4.1 Hydroesterification of Oleocompounds

The hydroesterification of oleic acid methyl ester was first described by Reppe [60]. He showed with the precursor $Ni(CO)_4$ at a reaction temperature of 280°C and a carbon monoxide pressure of $p_{CO} = 200$ bar a 36% yield of the hydroesterification product after 16 h.

The palladium-catalyzed hydroesterification of oleic acid methyl esters was investigated by Frankel and was conducted at lower reaction temperatures in comparison to the nickel catalysis [61]. For example, the hydroesterification of oleic acid methyl ester and methanol with $PdCl_2$ and PPh_3 was achieved at a pressure of 270 bar. A 62% yield of the hydroesterification product was achieved after 12 h. The new C–C bond was formed mostly at positions 9 and 10 of the carbon chain. Approximately 10% of the hydroesterification products were observed at positions C_8 and C_{11} to C_{13}, which could be attributed to isomerization of the double bond during the reaction.

Recent advances by Cole–Hamilton have shown that very high regioselectivity to linear diesters can be achieved in a palladium-catalyzed reaction using the special ligand DTBPMB [11, 62]. The double bond was isomerized along the chain, and the hydroesterification took place preferentially at the terminal carbon atom (Scheme 23).



Scheme 23 Isomerizing hydroesterification of methyl oleate

Several other terminal and internal olefins were used as model compounds in this reaction. 1-Octene, 2-octene, 3-octene, and 4-octene and methyl oleate showed very high selectivity for linear products. At 40°C and 20 bar CO pressure, 83% of the methyl oleate was converted to the linear α,ω-diesters with a 95% selectivity for linear products over 22 h.

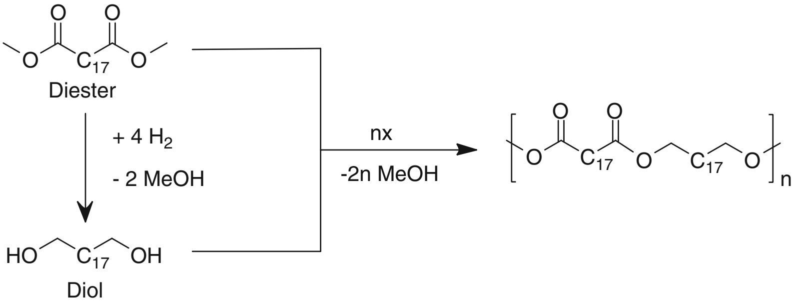
Mecking showed an efficient way to produce α,ω-diesters from fatty acid esters yielding excellent monomers for semicrystalline polyesters [63]. Some part of the diesters was hydrogenated to diols and was transesterified with the diesters from the hydroesterification of methyl oleate into long-chain polyesters (Scheme 24). The properties of this thermomorphic polymer are related to those of polyethylene.

4.2 Hydroesterification of Terpenes

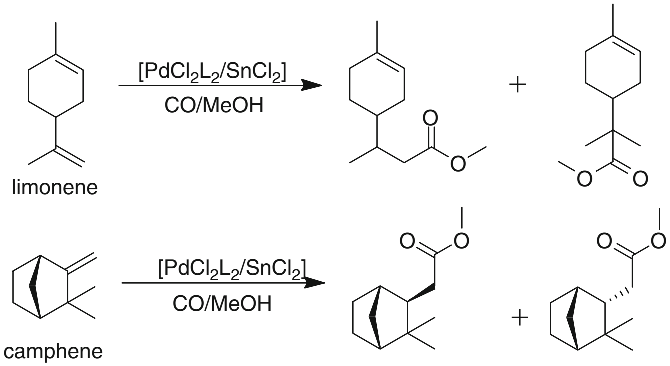
The hydroesterification of terpenes is attractive for access to odorous compounds and plasticizers. Gusevskaya showed an approach for the hydroesterfication of limonene and camphene [64] (Scheme 25).

With the tandem catalyst Pd/Sn, the hydroesterification of limonene delivered a 90% yield of the linear product, while in the absence of tin, more branched esters were formed. The hydroesterification of camphene delivers the linear product with a selectivity of 90%, whereas the two diastereomers were built in an equal ratio. The additive $SnCl_2$ had a high impact on catalytic activity; without this additive, the palladium/diphosphinobutane catalyst had lower activity.

The multiple C=C-double bonds in terpenes make it possible to functionalize the molecules at two or more sites. These products with two or more functional



Scheme 24 Polymerization of diols and diesters from the hydroesterification of methyl oleate



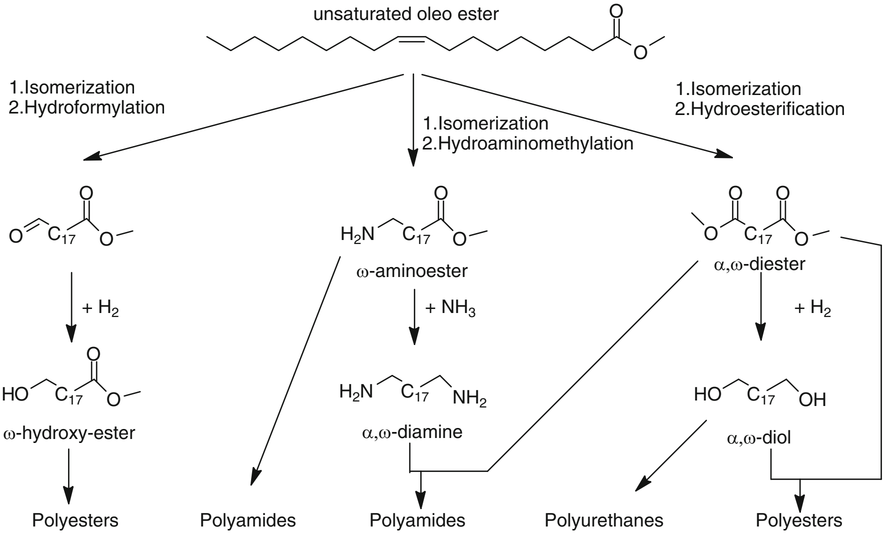
Scheme 25 Hydroesterification of limonene and camphene

groups are of interest for polymer applications which are being researched in our group. All three described reactions are promising for these functionalizations.

5 Conclusion

The applications of products from the hydroformylation and hydroesterification of oleocompounds and terpenes are growing and may soon become of great interest for industry. In the future, more technically applicable processes must be developed to make an economic breakthrough. Hydroaminomethylation is a very promising reaction for oleocompounds and terpenes and can yield interesting amino compounds.

The isomerizing functionalizations of unsaturated oleocompounds seem to be very attractive targets for the chemical industry. Scheme 26 affords a view into the (near?) future of a great number of polymeric compounds based on easily



Scheme 26 Possible polymer syntheses starting from oleocompounds

accessible oleochemicals: starting from different α,ω-functionalized compounds with carboxylic, ester and/or hydroxyl groups, numerous polyesters, polyamides, and polyurethanes can be made available. A similar development is possible also for terpenes.

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Catalytic Oxidation and Deoxygenation of Renewables with Rhenium Complexes

Ties J. Korstanje and Robertus J.M. Klein Gebbink

Abstract Transformation of renewables has received major research interest in recent years, opening up completely new research areas, in particular in the field of oxidation and deoxygenation. For the oxidation reaction, rhenium complexes, in particular methyltrioxorhenium, are well known for their potential as catalysts, but they are also potent catalysts for the deoxygenation reaction. The application of organometallic rhenium complexes in both the oxidation and deoxygenation reactions using a broad range of substrates derived from renewable resources, such as terpenes, oils, fats, lignin, and sugar alcohols, is reviewed in this chapter.

Keywords Dehydration • Deoxydehydration • Oxidation • Renewables • Rhenium complexes

Contents

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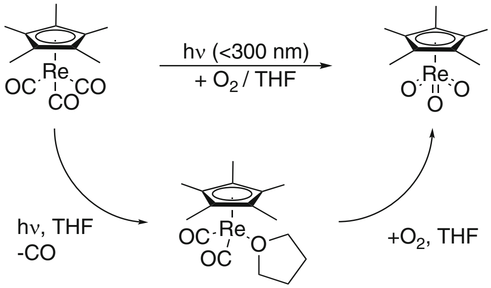
1 Introduction

Although organometallic rhenium oxide compounds have been known for more than 30 years, they have long been considered to be catalytically inactive species. However, in the beginning of the 1990s, the group of Herrmann found methyltrioxorhenium (CH_3ReO_3, MTO) to be an active catalyst in olefin metathesis [1], aldehyde olefination [2], and olefin epoxidation [3]. In the 20 years after, the class of organorhenium oxides has found application in a very broad scope of catalytic reactions.

One of the fields in which these organorhenium oxides have found application is in the field of biomass transformations. Two transformations have especially attracted much attention, i.e., oxidation and deoxygenation reactions, which especially high-valent organorhenium oxides can catalyze efficiently. One of the applications in oxidation reactions has focused on the epoxidation of various types of bio-based materials such as terpenes, oils, and fats, giving new and functionalized bio-derived building blocks useful for the chemical industry. Rhenium-catalyzed oxidative transformations such as oxidative cleavages or Baeyer–Villiger rearrangements have also been applied on renewables such as lignin, flavonoids, and nucleic and amino acids.

Rhenium-catalyzed deoxygenation reactions, on the other hand, can be divided in two topics: deoxydehydration and dehydration. These reactions have mostly been applied on biomass-derived substrates such as sugar alcohols and polyols. This procedure lowers the high O:C ratio present in biomass and as such is of particular interest for the production of both fuels and chemicals from biomass.

In this chapter, we have attempted to provide a comprehensive overview of the use of organometallic rhenium–oxo complexes in chemical transformations of biomass and biomass-derived compounds. The chapter starts with an overview of the discovery and history of homogeneous rhenium-based organometallic catalysts, ranging from the first discovery of a synthesis route to high-valent organorhenium oxides to the currently applied synthetic pathways (Sect. 1). Next, the use of these organorhenium(VII) oxides, with MTO as the most important example, in oxidation catalysis of olefins is described from a mechanistic viewpoint (Sect. 2), followed by their application as catalysts in the oxidation of various renewable starting materials (Sect. 3). Finally, the use of these complexes in the deoxygenation of biomass-derived alcohols and polyols, such as glycerol, erythritol, and other sugar alcohols, is described (Sect. 4).



Scheme 1 Synthesis of Cp*ReO$_3$ from Cp*Re(CO)$_3$ [6]

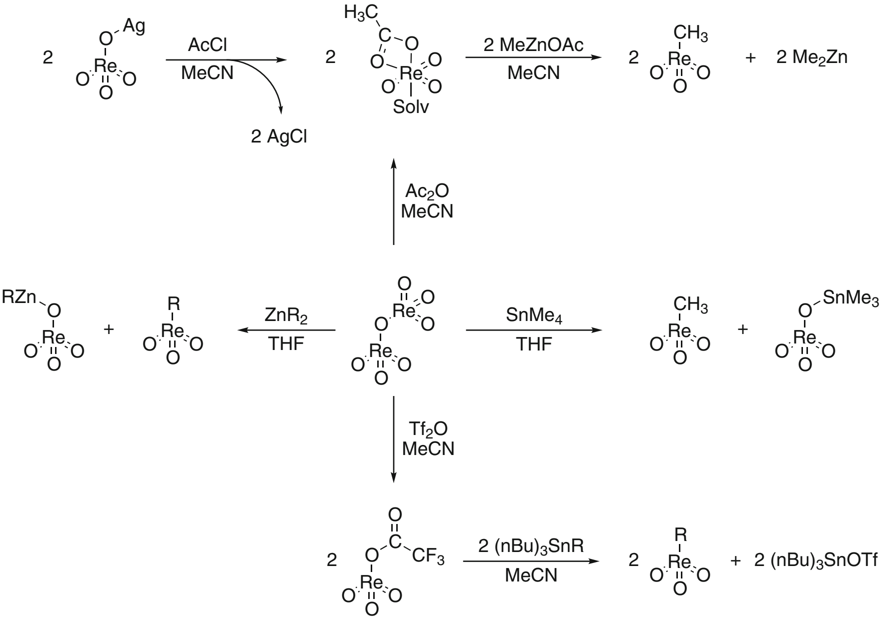
1.1 Synthesis of Organorhenium(VII) Oxides

The first attempts to synthesize organorhenium oxides date back to the early 1960s with attempts to synthesize (C_5H_5)ReO$_3$ [4], but it was only in 1979 that the first organometallic rhenium(VII) oxide, MTO, was successfully synthesized by Beatie and Jones via the oxidation of (CH_3)$_4$ReO in air for several weeks [5]. Five years later, two independent syntheses of η^5-($C_5(CH_3)_5$)ReO$_3$ (Cp*ReO$_3$) were reported by irradiation and subsequent oxidation in air or oxygen of the corresponding tricarbonyl compound (Scheme 1) [6, 7].

The synthesis of various organotrioxorhenium complexes was extensively studied in the years thereafter by the group of Herrmann, resulting in two major synthetic pathways (Scheme 2). One pathway proceeds via the reaction of rhenium(VII) oxide (Re_2O_7) with ZnR$_2$ at low temperature. This procedure has been first reported in 1989 and was found to be effective for the transfer of various phenyl [8, 9] and longer-chain alkyl groups [10, 11] to the rhenium center. However, this method was found to be ineffective for the transfer of other organic moieties.

In 1988, an alternative tin-mediated synthesis was found that involves the transfer of a methyl group from SnMe$_4$ to Re_2O_7, yielding MTO and trimethylstannyl perrhenate as the side product [12]. An adaptation to this reaction was achieved through the use of organotributyltin as the tin reagent. Via this route, various complexes of the formula RReO$_3$ were synthesized, with R = benzyl [13], R′O(O)C–CH$_2$– [13], allyl [13], indenyl [14], Cp [15], and alkynyl [16]. A disadvantage of using the tin route to synthesize these complexes is the loss of half of the starting amount of rhenium by the formation of tributylstannyl perrhenate. This can be easily overcome by treating Re_2O_7 with trifluoroacetic anhydride in acetonitrile to obtain (trifluoroacetyl)trioxorhenium, which can subsequently react with the trialkylorganotin reagent to obtain the desired organotrioxorhenium complex in very high yield based on rhenium.

Recently, an alternative synthesis route has been described that prevents the use of both the expensive and moisture-sensitive Re_2O_7 as well as of the toxic organotin compounds. This route uses acetyl perrhenate as the rhenium source and methylzinc acetate as the methylating agent. Acetyl perrhenate can be obtained by treatment of



Scheme 2 Synthesis of $RReO_3$ from Re_2O_7 via various routes

silver perrhenate with acetyl chloride and methylzinc acetate from the reaction of zinc acetate with trimethylaluminum. The only side products of the overall reaction are aluminum acetate (1/3 equivalent per rhenium) and silver chloride (1 equivalent per rhenium), which are both easily separated by filtration [17]. The different MTO synthesis methods are summarized in Scheme 2.

Unfortunately, many of the organometallic trioxorhenium complexes are light or temperature sensitive, rendering them poor catalysts. Of all the organotrioxorhenium complexes, only Cp^*ReO_3 and MTO have been found to be stable enough to perform well as catalysts and especially the latter is well known as an excellent olefin oxidation catalyst.

2 Methyltrioxorhenium as Catalyst in Olefin Oxidation

2.1 Mechanism and Active Species

Olefin oxidation is among the first catalytic applications found for MTO. The first reports showed good to excellent conversions of simple olefins, usually at room temperature, using hydrogen peroxide (H_2O_2) as the oxidant and *tert*-butanol as the solvent. Often a mixture of epoxide and *trans*-1,2-diol was obtained, which was attributed to the acidic nature of the reaction mixture (pH $\approx$ 1–2), resulting in ring

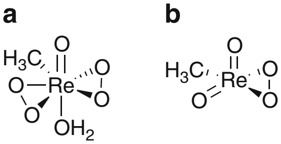


Fig. 1 The two active species in the MTO-catalyzed oxidation reaction: the bis(peroxo) (**a**) and mono(peroxo) (**b**) species

opening of epoxides to obtain *trans*-1,2-diols. This can be suppressed by the addition of an excess of amine to the reaction mixture, which lowers the proton activity (pH ≈ 4) and forms adducts with the MTO catalyst [3].

An important step toward understanding the mechanistic aspects of the MTO-catalyzed oxidation was made soon after with the discovery and isolation of the bisperoxo complex $CH_3Re(\eta^2\text{-}O_2)_2O(OH_2)$ (Fig. 1a). This complex is formed by treatment of MTO with an excess of H_2O_2 in either an organic solvent or water [11]. Its structure was determined in the solid state by X-ray diffraction as both the water/diglyme [18] and hexamethylphosphoramide (HMPA) adduct [19]. Both structures show a pentagonal bipyramidal configuration around the rhenium atom with the two peroxo ligands and the methyl group in the pentagonal plane and the oxo and diglyme/water or HMPA ligand in the axial positions. In solution, the water ligand is also bound to rhenium as shown by low-temperature (−55°C) NMR studies in THF-d_8. At room temperature, the water ligand exchanges with water present in the solution [20].

Next to the isolated bis(peroxo) species, it has also been shown that a mono (peroxo) species is present under epoxidation reaction conditions. The reaction of MTO with 1 equivalent of H_2O_2 yields the mono(peroxo) complex $CH_3Re(\eta^2\text{-}O_2)O$ (Fig. 1b), which is in equilibrium with MTO and the bis(peroxo) complex. The bis (peroxo) complex is the predominant species present in the reaction mixture, which is caused by a higher binding affinity of the second peroxo ligand compared to the first peroxo ligand. The binding of a second peroxo ligand is attributed to the higher electron deficiency of the mono(peroxo) complex with respect to MTO because of the presence of only one oxo ligand in the former [21]. In contrast to the bis(peroxo) complex, NMR studies of the mono(peroxo) complex do not indicate the presence of a stable aqua adduct in solution [20].

Kinetic experiments on the MTO/H_2O_2 system have indicated that both the mono- and bis(peroxo) species are active species in the olefin oxidation reaction. The rate constants of olefin oxidation by the mono- and bis(peroxo) species were found to be in the same order of magnitude, indicating that both complexes can be the predominant active species, depending on both the rate of formation of these species and the H_2O_2 concentration [20, 22].

These observations have been supported by DFT calculations on this system, indicating that the activation energies of the olefin epoxidation step from either the mono- or the bis(peroxo) complex are identical ($\Delta E^{\ddagger} = 16.2\ \text{kcal mol}^{-1}$), supporting the observation that both processes are equally relevant. In addition, the epoxidation step is proposed to take place via a nucleophilic attack of the olefin on a peroxidic oxygen atom, i.e., the peroxo complexes behave as electrophilic oxidants [23–25].

2.2 Influence of Lewis Base Adducts

Already in the first reports on olefin oxidation with the MTO/H_2O_2 system [3], it was noted that the formation of diols from the desired epoxides, caused by the Brønsted acidity of the system, is a major drawback of this system. The solution for this problem was found in the same report by the addition of a nitrogen base. This method has been explored extensively since and has become an important factor in the MTO-catalyzed olefin epoxidation.

Various nitrogen bases have been tested, among which quinuclidine, pyrazole, pyridine, 2,2′-bipyridine and its derivatives, and also various types of primary amines. All of these increase the selectivity for the epoxide greatly, although oxidation of the nitrogen base itself to the corresponding oxide has to be taken into account. Especially in the case of electron-rich aliphatic amines, which are oxidized much faster than aromatic nitrogen bases, this is a major problem, rendering them impractical as an additive in this reaction system [26]. Also in the case of pyridine, oxidation of the base is a problem since the MTO–pyridine *N*-oxide adduct is less selective than MTO itself. This can be overcome by using a large excess of the base as well as using a biphasic system in which the MTO–pyridine adduct dissolves in the organic phase (usually dichloromethane or nitromethane), while the formed pyridine *N*-oxide resides in the aqueous phase. Although this biphasic system enhances the reaction rate in some cases, the reaction efficiency is substrate-dependent [27, 28].

The effect of the nitrogen base can be attributed to a number of factors [26]. One of the factors is the basicity of the additive, which indicates that lowering of the activity of hydronium ions, which are responsible for the epoxide ring opening, is important. Another factor is the stabilization of MTO against decomposition, which is governed by both the basicity and the binding affinity of the base. A third factor involved is the effect of the base on the active species in the reaction, yielding a base rhenium–peroxo adduct that could be more active than the rhenium–peroxo complex itself. Among the various bases tested, it was found that pyrazole and 3-cyanopyridine are usually the most effective bases, although this can again depend on the substrate employed in the reaction [29, 30].

Since the addition of nitrogen bases was found to be advantageous for the epoxidation reaction, efforts have been made to synthesize rhenium complexes with C,N-chelating ligands. The first to report such a complex was the group of Herrmann [31], synthesizing a [3-(*N*-piperidyl)-*n*-propyl]trioxorhenium and a [3-(*N*,*N*-diethylamino)-*n*-propyl]trioxorhenium complex (Fig. 2). These chelating ligands however show a fluxional coordination behavior in THF solution above $-30°C$, and upon addition of quinuclidine, the intramolecular Re–N bond is broken in favor of the intermolecular rhenium–quinuclidine bond. Since the C,N-ligand contains an aliphatic amine moiety, which turned out to be very oxidation sensitive, these complexes are very poor oxidation catalysts.

The fact that phenyltrioxorhenium shows some activity in the oxidation reaction gave rise to the synthesis of a N,C,N-pincer trioxorhenium and a C,N-half-pincer

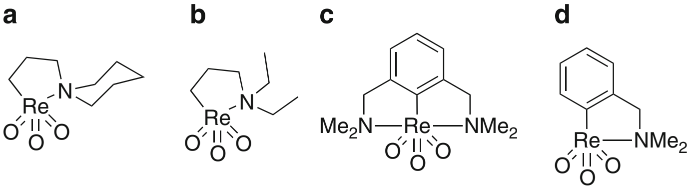


Fig. 2 Trioxorhenium complexes bearing C,N-chelating ligands

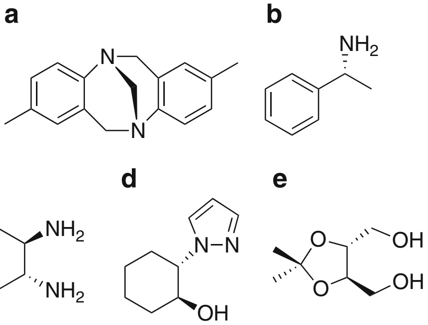


Fig. 3 Chiral bases used to carry out enantioselective MTO-catalyzed oxidation chemistry: Tröger's base (**a**), *R*-(+)-1-phenylethylamine (**b**), *trans*-(1*R*,2*R*)-1,2-diaminocyclohexane (**c**), *trans*-*N*-(2-hydroxycyclohexyl)pyrazole (**d**), and (−)-2,3-*O*-isopropylidene-D-threitol (**e**)

trioxorhenium complex in the group of Van Koten (Fig. 2) [32]. Neither of these complexes shows any activity in the oxidation reaction, probably due to the steric hindrance around the rhenium center as well as the low Lewis acidity of the rhenium atom.

An interesting opportunity that opens up with the use of nitrogen bases is the possibility of inducing chirality in the oxidation reaction. This was first recognized by the group of Herrmann, who reported on the use of Tröger's base (Fig. 3a) as the nitrogen base. While this system does show enhanced selectivity for epoxide formation as with similar nitrogen bases such as quinuclidine, it does not induce any chirality in the obtained epoxides. This can be explained by the weak rhenium–nitrogen interaction, caused by the low basicity of Tröger's base, and its low resistance to oxidation [33].

Several years later, the group of Corma reported on a successful study on stereoselective olefin epoxidation with MTO using various chiral nitrogen bases. Although the conversion is low (10%), an enantiomeric excess (ee) of up to 36% can be obtained with *cis*-β-methylstyrene as the substrate and *R*-(+)-1-phenylethylamine as base (Fig. 3b) [34]. Also, the groups of Saladino and Crucianelli used *R*-(+)-1-phenylethylamine as chiral base in a 1:1 ratio with MTO, forming the corresponding perrhenate salt, but also here, very low conversion is obtained. In the same report, the use of *trans*-(1*R*,2*R*)-1,2-diaminocyclohexane (Fig. 3c) in combination with MTO as catalyst and UHP as oxidant is mentioned. With this system in ethanol, full conversion of styrene is obtained, with 70% yield of epoxide and an ee of 13%. When using encapsulating the chiral complex in polystyrene (PS) (see Sect. 2.3 for more details on the encapsulation technique), a somewhat higher ee of 24% was obtained with 82% conversion and 75% yield of the epoxide [35].

A similar method, which uses chiral pyrazole derivatives, was reported in 2004 by the group of Kühn. Again, a low conversion was obtained (6%), but ee-values of up to 27% were observed with *cis*-β-methylstyrene using chiral *trans*-*N*-(2-hydroxycyclohexyl)pyrazole (Fig. 3d) as the base. In the same paper, the use of chiral diols is also discussed in order to obtain higher ee-values. The best-performing diol (Fig. 3e) again showed low conversion (5%) of *cis*-β-methylstyrene, albeit with an enantiomeric excess of 41% [36]. In all of these cases, it is noted that higher reaction temperatures and increased reaction times do increase the conversion but lower the enantiomeric excess. A major disadvantage of the use of chiral amines is the high excess needed to be effective, which is quite costly in most cases.

2.3 Immobilization of MTO

Although high activity and selectivity are of major importance for a catalyst to be successful, high turnover numbers (TON) are also highly relevant. Effective separation of the catalyst from the reaction mixture and successful recycling can be very important tools to enhance the TONs of a catalyst. For homogeneous catalyst systems such as the MTO/H_2O_2 system, this can be a big challenge. Therefore, much effort has been invested in the heterogenization of MTO onto a carrier material, which would greatly enhance the ease of recovery of the catalyst.

The group of Adam was the first to report on the use of a heterogenized MTO catalyst for oxidation chemistry using the urea/hydrogen peroxide (UHP) adduct [37]. This adduct is a polymeric solid containing helical channels, which does not dissolve in most organic solvents. It is proposed that the oxidation chemistry takes place in these channels, thereby resulting in high conversion and selectivity. The channels also protect the MTO catalyst from decomposition [38]. Another advantage of the use of UHP is its “anhydrous” nature, and accordingly no water other than that produced in the reaction is present, therefore lowering the chance on undesired epoxide ring opening.

A more widely used method of heterogenization has also been applied to MTO, by using a metal oxide support onto which the MTO is applied. MTO has been applied onto niobia (Nb_2O_5) both via impregnation and sublimation [39] and onto silica (SiO_2) via reaction of a bipyridine-containing siloxane [40]. In a similar manner, MTO has been immobilized on the mesoporous silica MCM-41 [41]. Zeolite NaY has been used as a support material by the in situ immobilization of the MTO catalyst [42].

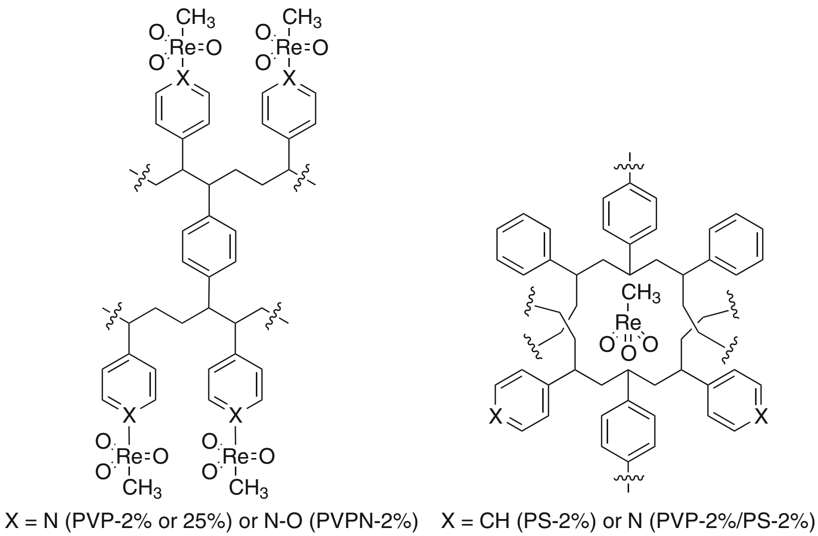


Fig. 4 MTO-containing polymers obtained via the microencapsulation technique [43]

A very interesting technique that has been used widely in the MTO-catalyzed olefin oxidation reaction is the microencapsulation technique. This technique uses poly(4-vinylpyridine) (PVP), either 2% or 25% cross-linked with divinylbenzene (PVP-2% or PVP-25%, Fig. 4), as well as poly(4-vinylpyridine-*N*-oxide) (PVPN-2%, Fig. 4). In addition, 2% cross-linked PS (PS-2%, Fig. 4, $X = CH_2$) and a mixture of PS-2% and PVP-2% (5:1, Fig. 4, $X = N$) have been used as support polymers. This approach is based on the physical envelopment of the Lewis-acidic MTO by the PS polymer, enhanced by interactions of the π-electrons of the phenyl rings with MTO. In the case of the pyridine-containing polymers, Lewis acid–Lewis base interactions between the pyridine moiety and MTO obviously play an important role. In the case of the PVP and PVPN polymers, MTO can be incorporated in the support matrix by mixing the polymer and MTO in ethanol to obtain the desired immobilized catalyst.

When using PS-based polymers, immobilization can be achieved by adding MTO to a THF suspension of the polymer. THF as a solvent causes sufficient swelling of the polymer for the MTO to be able to enter the pores, while after the reaction the polymers are shrunk by the addition of hexane, thereby encapsulating MTO. Using wide-angle X-ray scattering (WAXS), it was found that the MTO is coordinated to two pyridine rings and adopts an octahedral geometry, with bond lengths very similar to the ones found for the comparable homogeneous system, indicating that the MTO is barely influenced by the polymeric nature of the support [43].

The polymeric MTO adducts were tested in the oxidation of various olefins, among which *cis*-cyclohexene, and were very active and selective toward the epoxide, with the MTO/PVP-25% catalyst as the best performing in terms of both activity (>98% conversion after 30 min) and selectivity (>98% for the epoxide).

Recycling studies on these materials were performed by filtration of the heterogeneous catalyst from the reaction mixture. In most cases, almost no decrease in activity and selectivity was observed over five consecutive runs of oxidation of *cis*-cyclohexene to the corresponding epoxide. Only MTO/PS-2% shows a considerable decrease in activity during the five runs, dropping from >98% conversion with the fresh catalyst to 77% in the fifth run. Both MTO/PVP-25% and MTO/PVPN-2% have very good recycling characteristics, both preserving their high activity (89–98%) and selectivity (respectively 94% and 82%) during the five catalysis runs [43].

3 MTO-Catalyzed Oxidation of Renewables

3.1 Terpenes and Terpene Derivatives

Terpenes are a class of naturally occurring olefins found in many plants. They are biosynthetically derived from isoprene, C_5H_8, and therefore consist of C_5-building blocks and are found in both cyclic and acyclic forms. An important subgroup is the monoterpenes, which consist of two isoprene units and are of the molecular formula $C_{10}H_{16}$. Of the monocyclic monoterpenes, by far the most industrially relevant is limonene, which is abundantly present as a fragrance in various household products. From the bicyclic monoterpenes, α-pinene, β-pinene, camphene, and carene are of industrial relevance and are also mostly used in the fragrance industry [44].

3.1.1 α-Pinene

α-Pinene can be found in very high concentrations (up to 80%) in pine oil and can be isolated by distillation. Its main use in industry is as a starting compound for the synthesis of terpene alcohols such as terpineol and borneol or the terpene ketone camphor [44]. The epoxide of α-pinene is used as a starting compound for the synthesis of campholenic aldehyde [45] as well as *trans*-carveol [46], both of which are used in fragrancing.

Commonly, α-pinene is epoxidized to its oxide using organic peroxy acids such as *m*-chloroperbenzoic acid (*m*-CPBA). The main drawbacks of this method are the production of vast amounts of waste and the incompatibility with acid-sensitive epoxides, yielding the corresponding diol, sobrerol [47].

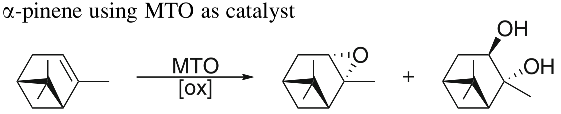
The first report on the oxidation of α-pinene with the MTO/H_2O_2 system comes from a patent of Herrmann in 1990 [48], where *tert*-butanol is used as the solvent without any additives. With this system at −30°C, 55% yield of the epoxide is obtained after 1 day. Several years later, an elaborate kinetic study was performed on the epoxidation of various olefins, but no yields or selectivities were given [49]. The first study on the optimization of this reaction was reported 2 years later by

Villa and coworkers [50]. The reaction was performed in several solvents in either the absence or presence of a nitrogen base. In THF at room temperature, with an α-pinene/MTO ratio of 200:1 and without any nitrogen base, a very low yield of epoxide is obtained caused by the fast ring opening of the epoxide under these conditions (Table 1, entry 2). Upon the addition of 100 equivalents of pyridine (per MTO), a major improvement was observed to 91% conversion and 69% product selectivity (entry 3). A switch to biphasic systems by using nitromethane as the solvent raises the yield and selectivity further, but the best results are obtained in dichloromethane with 24 equivalents of pyridine, yielding the desired epoxide in 90% after 2.5 h (entries 4 and 6). Also, 3-cyanopyridine was tested as nitrogen base in nitromethane, but only the rearrangement product α-campholenic aldehyde was found (entry 5). This is an interesting product in itself (vide supra), but unfortunately, a low product selectivity was found. The use of 2,2′-bipyridine as the nitrogen base in a biphasic system using CH_2Cl_2 as the solvent leads to a moderate conversion of 55% but with a complete selectivity for the epoxide [50, 51]. When no bipyridine is used, the conversion is higher but the selectivity a lot lower (entries 7 and 8). The diamine bases 2-aminomethylpyridine and *trans*-1,2-diaminocyclohexane have been found to give very efficient oxidation systems. In a CH_2Cl_2/CH_3CN mixture at room temperature, good conversions but low epoxide selectivities can be obtained with these bases. When lowering the temperature to −10°C, complete conversion and selectivity are obtained with both ligands (entries 9–11) [53].

Very recently, an extensive study on the influence of additives, oxidants, and solvents on the MTO-catalyzed oxidation of α-pinene was published (entries 12–15) [54]. By following the reaction in time and varying the amount of nitrogen base (in this case 4-*tert*-butylpyridine) at both 0°C and 25°C, it was found that the amount of α-pinene oxide increases rapidly in the beginning but decreases later on in the reaction, indicating that the oxidation is relatively fast compared to the hydrolysis of the epoxide. The best conditions use 20 equivalents of 4-*tert*-butylpyridine and a reaction temperature of 0°C to give an α-pinene oxide yield of 85% after 1.5 h (entry 12).

Next, the H_2O_2/MTO ratio was lowered from 300:1 to 150:1. The main effect is a much lower amount of diol formation but the same epoxide yield (entry 13). Lowering the amount of catalyst from 1 to 0.5 mol% and 0.1 mol% gives both a lower reaction rate and lower epoxide yield. Probably, this is caused by a higher rate of decomposition of the MTO catalyst as a result of the higher H_2O_2/MTO ratio. The use of different nitrogen bases gives no beneficial effect on the rate and selectivity, but switching to the UHP adduct as oxidant results in the suppression of diol formation and a somewhat higher epoxide yield (93%, entry 14). A subsequent solvent optimization showed the best epoxide yields in CH_2Cl_2, while for UHP, the highest activity was found in nitromethane. Finally, the conditions were re-optimized with UHP as the oxidant, and eventually, a full conversion of α-pinene to its oxide with complete selectivity was obtained, using nitromethane as the solvent and an α-pinene/MTO/4-*tert*-butylpyridine/UHP ratio of 200:1:40:600 at 0°C, reaching a turnover frequency (TOF) of 610 h^{-1} (entry 15).

Table 1 Catalytic results for the oxidation of α-pinene using MTO as catalyst



Entry	Solvent	Nitrogen base	S/Re/N/Ox[a]	T (°C)	t (h)	Conversion (%)	Selectivity (%)	Reference
1	*t*-BuOH	–	65:1:0:65	−30	24	NR[b]	55[c]	[48]
2	THF	–	200:1:0:220	rt	6	6	9	[50]
3	THF	Pyridine	200:1:100:460	rt	1.4	91	69	[50]
4	CH_3NO_2	Pyridine	200:1:100:420	rt	2.8	100	80	[50]
5	CH_3NO_2	3-Cyanopyridine	200:1:24:320	rt	1.7	NR[b]	0[d]	[50]
6	CH_2Cl_2	Pyridine	200:1:24:340	rt	2.5	100	90	[50]
7	CH_2Cl_2	–	100:1:0:150	rt	2	70	50	[51]
8	CH_2Cl_2	2,2′-Bipyridine	100:1:6:150	rt	1	55	99	[52, 53]
9	CH_2Cl_2/CH_3CN (1:1)	2-Aminomethylpyridine	100:1:1:150	rt	1.5	85	16	[53]
10	CH_2Cl_2/CH_3CN (1:1)	2-Aminomethylpyridine	100:1:1:150	−10	1.5	>98	>98	[53]
11	CH_2Cl_2/CH_3CN (1:1)	*trans*-1,2-Diaminocyclohexane	100:1:1:150	−10	1	>98	>98	[53]
12	CH_2Cl_2	4-*tert*-Butylpyridine	100:1:20:300	0	1.5	96	85	[54]
13	CH_2Cl_2	4-*tert*-Butylpyridine	100:1:20:150	0	3	84	96	[54]
14	CH_2Cl_2	4-*tert*-Butylpyridine	100:1:20:150[e]	0	24	NR[b]	93[c]	[54]
15	CH_3NO_2	4-*tert*-Butylpyridine	200:1:40:600[e]	0	24	100	100	[54]
16	CH_2Cl_2	3-Methylpyrazole/1-methylimidazole	500:1:50/5:1,000	10	4	>99	95	[55]
17	None	3-Methylpyrazole/1-methylimidazole	750:1:75/7.5:1,500	15	5	>99	91	[55]

[a] Ratio between substrate (α-pinene), MTO, nitrogen base, and oxidant (H_2O_2)

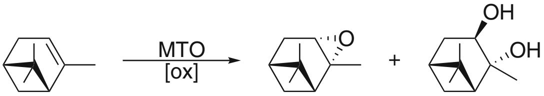
[b] Not reported

[c] Yield given

[d] 27% of α-campholenic aldehyde formed

[e] UHP used as the oxidant

Table 2 Performance of microencapsulated MTO–nitrogen base adducts in the oxidation of α-pinene[a]



Entry	Nitrogen base	T (°C)	t (h)	Conversion (%)	Selectivity (%)
1	–	rt	1.5	>98	>98
2	2-Aminomethylpyridine	rt	1.5	95	30
3	2-Aminomethylpyridine	−10	2	94	90
4	*trans*-1,2-Diaminocyclohexane	−10	1	>98	>98

[a] Reaction conditions: polystyrene microencapsulated MTO–nitrogen base adduct (loading of 1 wt%), CH_2Cl_2/CH_3CN (1:1), α-pinene/MTO/base/H_2O_2 ratio = 100:1:1:150 for monodentate bases or 100:1:0.5:150 for bidentate bases [53]

The use of 3-methylpyrazole combined with 1-methylimidazole as the nitrogen bases has also recently been explored, giving very good results at low catalyst loading (0.2–0.3 mol%). It was shown that with this system in neat conditions, the desired epoxide can be obtained in very good yield (91%) [55].

Finally, an interesting attempt has been carried out using chiral nitrogen bases in order to induce chirality in the oxidation reaction. Using (+)-2-aminomethylpyrrolidine as the chiral nitrogen base and UHP as the oxidant in CH_2Cl_2 at −5°C, a moderate diastereomeric excess of 41% is obtained at 11% conversion of α-pinene. This study shows the feasibility of inducing enantioselectivity in this reaction by means of the use of chiral amine bases [34].

As described in Sect. 2.3, immobilized MTO complexes are used in oxidation chemistry, and α-pinene is also used as a substrate with these catalysts. The group of Saladino reported the use of MTO–nitrogen base adducts microencapsulated in PS beads (Table 2) [53]. First, microencapsulated MTO was used without nitrogen base, giving excellent results with complete conversion and selectivity toward the epoxide (entry 1) [56]. Then, 2-aminomethylpyridine was used as the nitrogen base, and somewhat poorer results were obtained, showing somewhat lower conversion and selectivity (entries 2 and 3). However, the adduct with *trans*-1,2-diaminocyclohexane shows the same results as without a nitrogen base, complete conversion and selectivity for the epoxide within 1 h at −10°C (entry 4) [53]. Although the use of a nitrogen base adduct is not necessary to obtain good results in the oxidation of α-pinene, it might have a positive effect on the stability of the catalyst. The stability of MTO/PS-2% was tested in the epoxidation of geraniol (vide infra), and this catalyst shows some decrease in both conversion and selectivity after five runs [56]. The *trans*-1,2-diaminocyclohexane adduct of this catalyst, on the other hand, shows no deterioration after five runs in the epoxidation of cyclooctene [53].

The immobilization of MTO on poly(vinylpyridine) or its oxide was also tested, but here, the conversions are a bit lower [56]. Furthermore, the effect of comonomers in PVP, such as butylmethacrylate or ethyleneglycoldimethacrylate, was explored. With some of these systems, excellent selectivity for the epoxide was

Table 3 Results on the MTO-catalyzed oxidation of β-pinene

Entry	Solvent	Nitrogen base	T (°C)	t (h)	Conversion (%)	Selectivity (%)	Reference
1	t-BuOH	–	5	0.1	NR	40	[3]
2	CH_2Cl_2	–	0	0.5	60	90	[51]
3	CH_2Cl_2	Pyridine[a]	0	1.5	98	84	[50]
4	CH_2Cl_2	3-Methylpyrazole[b]	10	1.5	>99	92	[55]
5	CH_2Cl_2	3-Methylpyrazole/ 1-methylimidazole[c]	10	2.5	>99	94	[55]
6	None	3-Methylpyrazole/ 1-methylimidazole[c]	10	6	>99	82	[55]

[a] Ratio of substrate/MTO/nitrogen base/H_2O_2 = 200:1:84:300
[b] Ratio of substrate/MTO/nitrogen base/H_2O_2 = 500:1:5:600
[c] Ratio of substrate/MTO/nitrogen base/H_2O_2 = 500:1:50/5:600

obtained, but always at very low conversion (<10%). An optimization toward α-campholenic aldehyde was also performed, and here, very good selectivities toward the aldehyde can be obtained, yet again only at a very low conversion [57].

3.1.2 β-Pinene

β-Pinene is the minor pinene isomer in turpentine oils and can be obtained by distillation. It is very similar in its chemistry to α-pinene, and its most important industrial application is the production of myrcene by pyrolytic cleavage [44, 45]. The epoxide of β-pinene can be used to produce perillyl alcohol, a compound with known antimicrobial activity, and myrtanal, an aldehyde found in the plant *Paeonia* taxa, which is used as antiseptic and for cleaning wounds [58].

β-Pinene is one of the olefin substrates that was tested in the first paper on MTO-catalyzed olefin oxidation in 1991 [3]. Here, a monophasic system of *tert*-butanol with H_2O_2 was used and already after 6 min at 5°C 40% selectivity toward the epoxide and 50% selectivity toward the diol was observed (Table 3, entry 1), pointing out the high acid sensitivity of the epoxide. Later on, a biphasic system was reported, using CH_2Cl_2 as the solvent, giving a moderate conversion at 0°C after 0.5 h but with a good selectivity (entry 2) [51]. When pyridine is used as the nitrogen base, almost full conversion is obtained in only 1.2 h at 0°C and a good selectivity of 84%, while 11% of rearrangement products were noted (entry 3) [50]. The use of 3-methylpyrazole as the nitrogen base results in complete substrate conversion with a very high product selectivity (92%) after 1.5 h (entry 4). The additional use of 1-methylimidazole leads to a somewhat higher selectivity, while leaving out the organic solvent under these conditions still leads to a selectivity of 82% at full conversion (entries 5 and 6) [55].

3.1.3 Limonene

Limonene is a monocyclic terpene, bearing two C–C double bonds. Its (+)-enantiomer is the major constituent (>90%) of citrus peel oils and is therefore obtained in large quantities as a side product from orange juice production. The (−)-isomer however is only isolated in relatively small quantities from essential oils [44]. The major usage of limonene is in the production of carvone and as a fragrance in itself [47]. A very interesting application for limonene oxide has been reported in the synthesis of a high-molecular-weight polycarbonate by copolymerization with CO_2 [59].

The fact that limonene is a diene makes oxidation chemistry more complicated since usually the monoepoxide is desired. The first report of MTO-catalyzed oxidation of limonene is described in a patent by Herrmann in 1990 [48], using *tert*-butanol as the solvent and obtaining the 1,2-epoxide in 35% yield after 5 h at room temperature (Table 4, entry 1). In this case, a biphasic aqueous system was used with CH_2Cl_2 as the organic phase, which greatly improves the reaction to give high conversion and selectivity for the 1,2-epoxide (1:1 *cis-*/*trans*-mixture) after 1 h at 4°C [51] or after 30 min at room temperature (entries 2 and 3) [60]. The addition of pyridine as the nitrogen base shifts the selectivity completely toward the diepoxide (entry 4), while the use of THF as a solvent and a mixture of pyridine and 3-cyanopyridine as the nitrogen base gives moderate results (entry 5) [50].

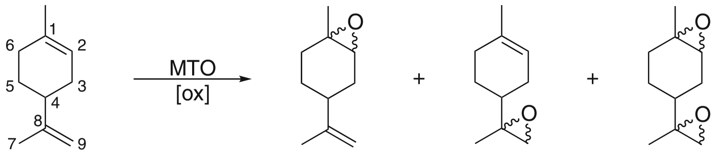
As with α-pinene, a very well-performing system can be obtained by using either 2-aminomethylpyridine or *trans*-1,2-diaminocyclohexane as the nitrogen base in a CH_2Cl_2/CH_3CN solvent mixture (entries 6 and 7). Especially, the latter gives excellent results with full conversion and selectivity for the monoepoxide [53].

Finally, two interesting systems with nonconventional solvents were reported. One uses the ionic liquid 1-butyl-3-imidazolium tetrafluoroborate ([BMIM][BF_4]), giving results quite similar to those in CH_2Cl_2 with a large excess of pyridine, with good conversion and selectivity for the diepoxide (entry 8) [61]. The other nonconventional solvent used is the fluorous solvent hexafluoro-isopropanol. In the presence of 2,2′-bipyridine, this system gives full conversion and selectivity at a very low catalyst loading of 0.1 mol% (entry 9) [62].

Yamazaki recently reported on a system using 3-methylpyrazole in CH_2Cl_2 with very low catalyst loadings of 0.2 mol% MTO, giving the diepoxide as the product in near quantitative yield (entry 10). Using the same system, but without any organic solvent, a faster reaction and completely different selectivity was obtained, with the 1,2-epoxide as the preferential product (entry 11) [55].

A single report describes the use of a different rhenium catalyst than MTO in the catalytic oxidation of limonene. This catalyst consists of a rhenium(V) complex bearing two picolinato ligands. This complex, shown in Fig. 5, was synthesized by the addition of MTO to an aqueous solution of picolinic acid and was also found to activate H_2O_2 by forming a peroxo rhenium species as determined by Raman spectroscopy. This complex gives very comparable results as MTO in CH_2Cl_2 with good conversion and selectivity (entry 12). Raman measurements under

Table 4 Results of MTO-catalyzed oxidation of limonene



Entry	Solvent	Nitrogen base	*T* (°C)	*t* (h)	Limonene/MTO/base/H_2O_2	Conversion (%)	Selectivity (mono/di, %)	Reference
1	*t*-BuOH	–	rt	24	65:1:0:65	NR[a]	35[b]	[48]
2	CH_2Cl_2	–	4	1	100:1:0:150	92	93	[51]
3	CH_2Cl_2	–	rt	0.5	200:1:0:400[c]	99	100/0	[60]
4	CH_2Cl_2	Pyridine	0	6	100:1:84:130	100	0/90	[50]
5	THF	Pyridine/3-cyanopyridine	0	2.3	200:1:24/170:220	96	82/14	[50]
6	CH_2Cl_2/CH_3CN (1:1)	2-Aminomethylpyridine	−10	2	100:1:1:150	98	85/0	[53]
7	CH_2Cl_2/CH_3CN (1:1)	*trans*-1,2-Diaminocyclohexane	−10	1	100:1:0.5:150	>98	>98/0	[53]
8	[BMIM][BF_4]	–	rt	2	20:1:0:40	>98	10/88	[61]
9	$(CF_3)_2CHOH$	2,2′-Bipyridine	0	1	1,000:1:100:2,000	100	100/0	[62]
10	CH_2Cl_2	3-Methylpyrazole	10	8	500:1:50:1000	100	1/98	[55]
11	None	3-Methylpyrazole	10	3	500:1:50:1000	97	83/14	[55]
12	CH_2Cl_2	Picolinic acid[d]	4	2	100:1:2:150	94	93	[63]

[a] Not reported
[b] Yield given
[c] UHP used
[d] $CH_3ReO(pic)_2$ used as catalyst

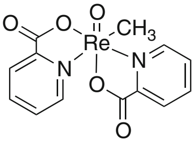


Fig. 5 Structure of methyloxorheniumbis(κ^2-picolinato) [63]

experimental conditions showed the appearance of various rhenium-peroxo species, but the exact nature of the active species is not known [63].

In the limonene oxidation reaction, various immobilized systems have been tested as catalyst. The use of MTO supported on poly(vinylpyridine) polymers however turned out to be a poor system for the limonene oxidation since both the conversions and the selectivities were quite a bit lower than the optimal non-immobilized system [56]. These systems were also used in combination with ionic liquids, and here, a similar result as with the non-immobilized system was found, yielding mostly diepoxide, with the best-performing catalyst MTO/PVP-25% in [BMIM][BF$_4$], giving 92% of diepoxide at full conversion [61].

The system based on MTO–nitrogen base adducts microencapsulated in PS gives very similar results as the nonencapsulated system, resulting in nearly complete conversion and selectivity for the monoepoxide, making this a very powerful system for epoxidations [53].

Another immobilized system was recently reported by Wei and Liu [64] using amphiphilic coblock polymers consistent of ethylene glycol and methyl acrylate monomers that had been functionalized with imidazole groups. In combination with oxone (KHSO$_5$) as the oxidant in an ethyl acetate/water mixture, this system yields the 1,2-diol product in 62% yield, which is probably formed by ring opening of the epoxide by the acidic oxone.

3.1.4 Other Terpenes

Among the other terpenes that have been used as substrate in the MTO-catalyzed oxidation reactions are the bicyclic monoterpenes carene and camphene, the acyclic monoterpene myrcene, β-citronellene (the reduced form of myrcene), and the bicyclic sesquiterpene β-caryophyllene (Fig. 6).

Carene was found to be easily and selectively oxidized with the biphasic system using CH_2Cl_2 as the solvent, obtaining nearly complete conversion and full selectivity for the epoxide after 2 h at 4°C [52], while upon addition of pyridine, the selectivity drops to 75% [56]. When changing the solvent to the ionic liquids [BMIM][PF$_6$] or [BMIM][BF$_4$], again full conversion and selectivity are obtained without any added nitrogen base [61]. When applying neat conditions and 3-methylpyrazole together with 1-methylimidazole as the nitrogen base, full conversion and selectivity are obtained at 10°C at low catalyst loading (0.3 mol%) [55].

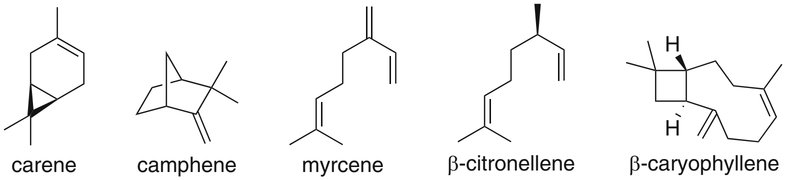


Fig. 6 Other terpenes oxidized with the MTO/H_2O_2 system

The best-performing immobilized catalyst system for carene oxidation to date is MTO/PVP-25% in a CH_2Cl_2/CH_3CN mixture, reaching complete conversion and excellent selectivity toward the epoxide in 2.5 h at room temperature [56]. The microencapsulated MTO in PS also performs well, and upon addition of the nitrogen base *trans*-1,2-diaminocyclohexane, even complete conversion and selectivity are obtained in only 30 min at −10°C. When using an ionic liquid as solvent and UHP as the oxidant, both the PVP-immobilized MTO catalyst and PS-immobilized MTO show excellent performance. When performing recycling experiments with MTO/PVP-25%, it was however found that the selectivity drops to values around 90% after two runs [61].

The oxidation of camphene is somewhat more difficult. Using deuterated chloroform as the solvent and H_2O_2 as the oxidant, a low conversion is obtained after 3 h (27%), and only cleavage and rearrangement products are formed. When switching to UHP as the oxidant, a very good conversion of 92% is obtained after 30 h with complete selectivity toward the epoxide [37].

With myrcene and β-citronellene, different results are obtained: myrcene can be oxidized at the internal double bond with full conversion and good selectivity (90%), while β-citronellene is oxidized at the same bond with significantly inferior characteristics (72% conversion, 50% selectivity). The major side product in the latter case is the diepoxide, which does not occur in myrcene because of stabilization of this double bond via conjugation [52].

Finally, β-caryophyllene was also subjected to the MTO-catalyzed oxidation. Here, the biphasic system with CH_2Cl_2 as the solvent is very effective, with full conversion and selectivity for the internal epoxide after only 1 h of reaction time and a very low catalyst amount of 0.1 mol%, using a 10:1 mixture of 3-methylpyrazole and 1-methylimidazole as nitrogen base [55].

3.1.5 Terpene Alcohols

Acyclic monoterpene alcohols are present in many essential oils and can be isolated by distillation, although nowadays, they are often synthesized from other sources. Geraniol and linalool (Fig. 7) are the most important monoterpene alcohols and together with nerol are the primary products in terpene biosynthesis [44]. α-Terpineol is a frequently used cyclic monoterpene alcohol in the fragrancing industry because of its typical lilac odor and is also partly responsible for the typical

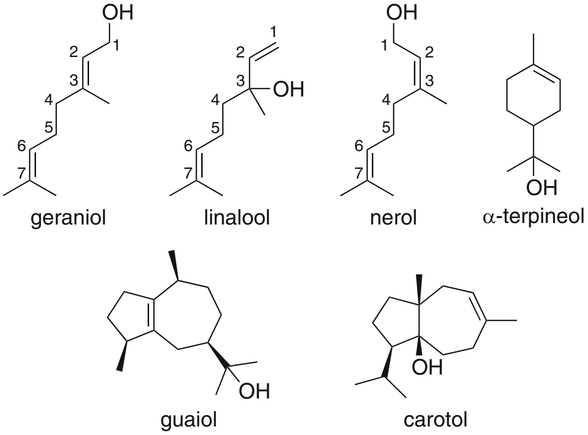


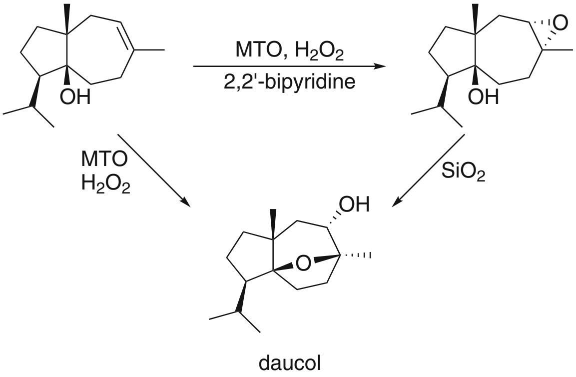
Fig. 7 Monoterpene alcohols geraniol, linalool, nerol, and α-terpineol and sesquiterpene alcohols guaiol and carotol

smell of lapsang souchong tea [65]. Although it is found in essential oils, it is usually synthesized from α-pinene via complete hydration to terpin hydrate and subsequent partial dehydration [44]. The oxidation product geraniol oxide can be used as a starting compound in the synthesis of antibiotics [66], and both linalool oxide and nerol oxide are much used fragrances because of their floral smell.

The sesquiterpene alcohol guaiol is found in wood from the tree *Bulnesia sarmienti* Lorentz, growing in Paraguay and Argentina. It can be used as a starting compound for guaiazulene, which has anti-inflammatory properties. Carotol, another sesquiterpene alcohol, is the major constituent (>50%) of carrot seed oil, which is used in the alcoholic beverages industry and fragrance and flavor industry [44].

Oxidation of these monoterpene alcohols has been carried out with the biphasic MTO/H_2O_2 system in CH_2Cl_2 in the presence of pyridine with very good conversions but moderate selectivities. With a 1:1 ratio of substrate and oxidant, the selectivity for the monoepoxide is 76–78% (6,7-epoxide/2,3-epoxide ratio = 11:1) with some diepoxide present. Predominant diepoxide formation was found at a 1:2.8 ratio of substrate to oxidant with geraniol and nerol as substrates (respectively, 61 and 87% selectivity with full conversion) [50]. Switching the oxidant to UHP did not make any difference, while switching to ethanol as the solvent only yielded decomposition products and diepoxide [60].

Geraniol has also been subjected to oxidation in a solventless system, using 3-methylpyrazole as the nitrogen base and a catalyst loading of 0.2 mol%. Good conversion is obtained after only 30 min with 80% selectivity for the 6,7-epoxide, while 15% of diepoxide is formed [55]. In the case of linalool, the 1,2-double bond is not oxidized even at higher oxidant loadings, but another side product is formed by intramolecular cyclization, forming a pyran ring. When the hydroxy moiety in linalool is protected with an acetate group, the selectivity for the 6,7-epoxide rises to 96%. Also geranyl and neryl acetate can be oxidized, but only at the higher oxidant conditions, yielding a mixture of mono- and diepoxide. When using THF as the solvent and a mixture of pyridine and 3-cyanopyridine as the base, selectivities for the monoepoxide of 85% and 89% are reached [50].



Scheme 3 Oxidation of carotol to its *trans*-epoxide and the acid-catalyzed rearrangement product daucol [51]

The use of various immobilized systems in a CH_2Cl_2/CH_3CN mixture gives mostly the same results in the oxidation of geraniol and nerol, with high conversions (89 to >98%) but selectivities for the 6,7-epoxide of 66–88%, with MTO/PVPN-2% as the best-performing system. The oxidation of geraniol was used to test the recyclability of these systems, and all catalysts show a stable performance over five runs, except for MTO/PS-2%, which shows a drop in conversion from 96% to 81% and in selectivity from 82% to 75% [56]. The same catalysts have also been tested in ionic liquids, but here, the selectivities for the 6,7-epoxide do not exceed 86% [61].

The cyclic monoterpene alcohol α-terpineol can be oxidized using CH_2Cl_2 as the solvent, and good results are obtained with 3-methylpyrazole as the nitrogen base and MTO as catalyst at low loadings (0.1 mol%). After 1 h full conversion and 94% selectivity for the epoxide are obtained, but when the reaction time is elongated, ring opening of the epoxide and also rearrangement to 2-hydroxy-1,8-cineol are observed. When adding 1-methylimidazole as the nitrogen base, the rearrangement process is mostly suppressed and after 1.5 h, a somewhat higher selectivity (97%) is obtained. When using these nitrogen bases in solvent-free conditions, the reaction proceeds very smoothly with similar results after 2 h at even lower catalyst concentration (0.05 mol%) [55].

Upon subjecting the sesquiterpene alcohol guaiol to the biphasic MTO-catalyzed oxidation with UHP, 96% conversion to the epoxide is obtained with an α/β ratio of 9:1, clearly showing a preference for the sterically less hindered side of the bicyclic compound. In a monophasic system with ethanol and H_2O_2, a similar result is obtained [60]. In the case of carotol, a clear acid sensitivity is found, as the reaction in the biphasic system quantitatively yields daucol, which is not an epoxide but a tricyclic compound with a 1,4-oxide-bridge (Scheme 3). When 2,2′-bipyridine is added, the expected *trans*-epoxide is formed with high conversion (95%) and selectivity (85–90%). Upon attempts to purify this compound via column chromatography, again daucol was obtained, which pointed out that even a mild acid such as silica gel is able to promote the rearrangement of the epoxide toward daucol [51].

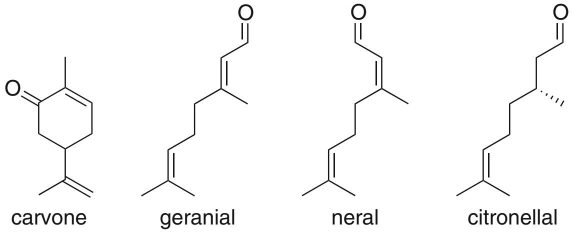


Fig. 8 Monoterpene ketones carvone, geranial, neral, and citronellal; together geranial and neral make up citral

3.1.6 Monoterpene Ketones

As with the monoterpene alcohols, their ketones are found in many essential oils. Carvone (Fig. 8), for instance, is found in high concentrations in either caraway oil [the (+) enantiomer] or spearmint oil [the (−) enantiomer], although industrially, it is usually synthesized from limonene [44]. Its epoxide is used as a fragrance but has also been found to be effective as an anticonvulsant drug for use with epilepsy patients [67]. Citral, a mixture of geranial and neral, is found in high concentrations in lemongrass oil but can also be synthesized by vapor-phase or catalytic dehydrogenation of geraniol and nerol. Citral is a starting material for vitamin A production and is therefore produced on a large scale. Citronellal is currently produced from the essential oil from *Eucalyptus citriodora* and is mostly used to synthesize (−)-menthol [44].

Carvone can be oxidized by the MTO/H_2O_2 system with the original procedure by Herrmann using *tert*-butanol as the solvent. After 18 h at 5°C, a conversion of 85% with a selectivity of 98% for the epoxide of the terminal (8,9) double bond is obtained [68]. Using the same procedure, citral is oxidized in a mere 28% yield of the 2,3-epoxide [48]. When using the biphasic system with CH_2Cl_2, however, full conversion and selectivity for the epoxide are obtained after 3 h at 0°C. Unfortunately, it was not specified which epoxide is formed. This biphasic system is also very effective for the oxidation of citronellal, giving nearly full conversion and selectivity for the epoxide after 2 h at 4°C [51].

3.2 Oils and Fats

One of the renewable resources that is very important for the chemical industry and is produced at a very large scale is the group of oils and fats. Oils and fats, either from animal or vegetable origin, are of course primarily used for food purposes, although their use for industrial purposes has increased a lot in the last decade, mostly because of the growing production of biodiesel [69].

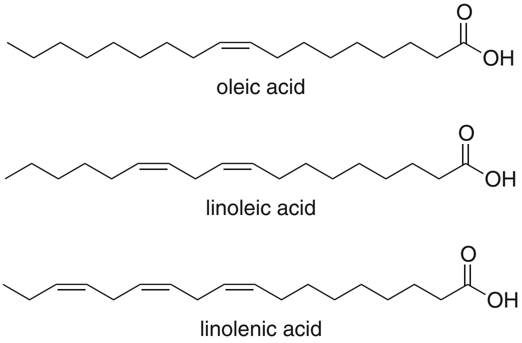


Fig. 9 Commonly found unsaturated fatty acids: oleic acid, linoleic acid, and linolenic acid

The most produced oils and fats are palm and palm kernel oil, soybean oil, and rapeseed oil, and of these, palm and rapeseed oil are mostly used for biodiesel production. The major components of these oils are saturated fatty acids with C8–C18 chain lengths and unsaturated C18 fatty acids, such as oleic acid (one double bond, Fig. 9), linoleic acid (two double bonds) and linolenic acid (three double bonds), which all contain *cis* double bonds only. In palm oil, the major unsaturated constituent is oleic acid (39%) followed by linoleic acid (11%), while in soybean oil, linoleic acid is the major constituent (54%) followed by oleic acid (22%) and linolenic acid (8%) [70].

These fatty acids and oils, as well as their derivatives, are applied in a broad range of products such as surfactants, lubricants and coatings, and, obviously, biodiesel. Upon epoxidation of the double bonds of the unsaturated fatty acids, very important compounds for the polymer industry are produced, which are used as plasticizers and stabilizers for a broad range of polymers such as polyvinyl chloride (PVC), polyesters, and polyurethanes [71]. Another interesting application has been found in the conversion of epoxidized soybean oil to carbonated soybean oil that can be reacted with ethylene diamine to obtain a polyurethane with interesting properties [72]. Traditionally, stoichiometric reagents are used for the epoxidation of these oils and fats, albeit in some cases, with limited results. Therefore, the MTO/H_2O_2 system has been explored to epoxidize unsaturated fatty acids and oils.

3.2.1 Soybean Oil

The first report of MTO-catalyzed epoxidation of oils dates from 1999 by Refvik and Larok [73] with the epoxidation of soybean oil under aqueous biphasic conditions using CH_2Cl_2 as the organic phase. With 1 mol% of MTO and 12 mol % of pyridine, soybean oil is completely epoxidized within 2 h at room temperature. In a larger-scale (100 g) experiment with half the amount of catalyst and base, complete epoxidation is obtained after 24 h [71, 73]. Two other reports have elaborated on this study, investigating more thoroughly the reaction products and applying different nitrogen bases [74, 75]. It was found that pyridine outperforms all other tested nitrogen bases. When using pyrazole or 2,2′-bipyridine dioxide, which in other epoxidation reactions showed very good results, even poorer results than in the absence of base are obtained [74]. Imidazole was the only base found to give similar results as pyridine [75].

An interesting system that is applied in the epoxidation of soybean oil is MTO immobilized on niobia combined with UHP as oxidant. The different components of soybean oil have been studied separately, and it was found that oleic acid can be epoxidized completely with 1 mol% MTO/Nb_2O_5 in 2 h at room temperature. When raising the temperature to 50°C and lowering the catalyst amount to 0.2 mol%, complete epoxidation is reached in as little as 10 min. In applying the same procedure to linoleic and linolenic acid, excellent yields of epoxidized product are obtained within 30 min. In attempts to reuse the catalyst in this reaction, it was found that the catalyst remains active for three runs, although no numerical data is provided to underline this [39, 76].

3.2.2 Other Oils and Fatty Acids

A class of animal oils that has been used as substrate for the MTO-catalyzed epoxidation reaction is fish oil. Because of its animal origin, the composition of fish oil varies with the type of fish and with its geographical origin. Two types of fish oil have been used, one from Norway in the ethyl ester form and the other from Icelandic capelin in the triglyceride form. The Norway fish oil is highly unsaturated, containing 3.6 double bonds per ester moiety (based on NMR spectroscopy), while the capelin oil contains 4.5 double bonds per triglyceride, i.e. 1.5 per fatty acid chain. It was found that the capelin oil is mainly consistent of saturated and monounsaturated fatty acids (respectively 23% and 61%), while the Norway fish oil contains a lot of higher unsaturated fatty acids (36% of pentaunsaturated and 25% of hexaunsaturated fatty acid). Both these oils yield completely epoxidized samples after 6 h using MTO/H_2O_2/pyridine in biphasic conditions in, respectively, 86% and 72% yield [77].

Another oil used for epoxidation with MTO/H_2O_2 is the oil from *Jatropha curcas* L. also known as Barbados or Physic nut. As with palm oil, it mostly consists of oleic acid (50%) and linoleic acid (29%) and various saturated fatty acids (20%). With 0.5 mol% of MTO and 12 mol% of pyridine in biphasic conditions, it was found that Jatropha oil can be completely epoxidized within 1.5 h [78].

One paper from the group of Zhang reports [75] on the testing of various oils with MTO/H_2O_2 with CH_3CN as solvent and imidazole as the nitrogen base. A base/MTO/H_2O_2/double bond ratio of 50:1:250:100 is used, and excellent results are obtained after 2 h at room temperature. Fatty acid methyl ester, sunflower oil, rapeseed oil, cottonseed oil, and palm oil can all be epoxidized with >99% selectivity and >98% yield with this system.

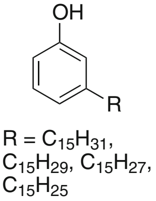


Fig. 10 Cardanol oil

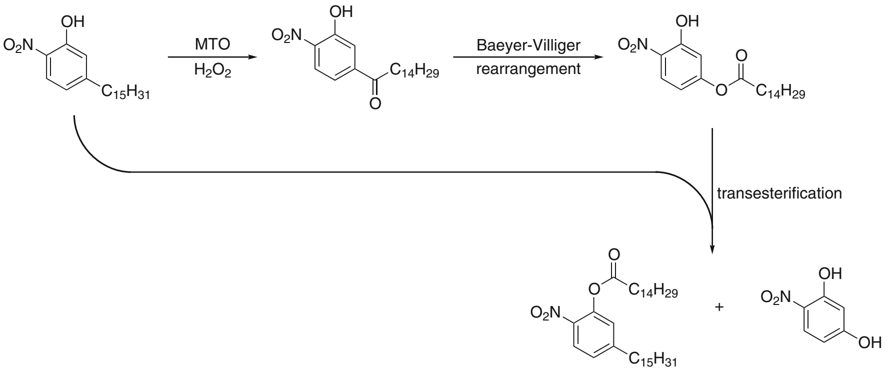
The use of isolated fatty acids as substrates for epoxidations has already been reported in 1990 with the epoxidation of methyl oleate and methyl linoleate by MTO/H_2O_2 in *tert*-butanol. After respectively 24 and 2 h, good yields of either the corresponding diol (methyl oleate) or the monoepoxide (methyl linoleate) are obtained (respectively 92% and 80%) [48]. Under biphasic conditions, the MTO-catalyzed epoxidation of methyl linoleate yields a mixture of mono- and diepoxide (approximately 1:1) at complete conversion after 6 h [79]. Finally, a conjugated methyl linoleate is treated with the MTO/H_2O_2 system in biphasic conditions, but here, poor results are obtained after 24 h at room temperature, yielding 26% of the 11,12-monoepoxide and 20% of the 9,10-epoxide [80].

3.2.3 Cardanol Oil

Another source of oil, but of very different composition than the previously described oils, is cardanol oil, the major component of cashew nut shell liquid. This is a low-value side product of the mechanical processing of the cashew nut and is therefore a widely available source of cardanol oil. Cardanol oil is a mixture of 3-pentadecylphenol with either a saturated alkyl chain or a one-, two-, or threefold unsaturated alkyl chain (Fig. 10).

Already in 1994, it was reported that substituted phenols can be oxidized with MTO/H_2O_2 to obtain *para*-benzoquinones [81]. Benzoquinones are interesting compounds due to their ubiquity in nature and biological importance.

In 2000, the first oxidation of cardanol oil with MTO/H_2O_2 was reported, where 3-*n*-pentadecylphenol, obtained from distillation of hydrogenated cardanol oil, is used as the substrate. Using MTO in 2 mol% amount and H_2O_2 as the oxidant in ethanol, a poor yield of 35% of 4-pentadecyl-1,2-benzoquinone as the only product is obtained. When switching to acetic acid as the solvent, the yield increases to 51%, and when adding an excess of HBF_4 in ethanol, the yield increases further to 75%, without the formation of any side product. The latter observation is interesting since the oxidation of 3-methylphenol yields *para*-benzoquinone as the only product. Probably, the long alkyl chain provides sufficient steric hindrance to prevent 3-*n*-pentadecyl-1,2-benzoquinone or 3-*n*-pentadecyl-1,4-benzoquinone to be formed [82]. Immobilized MTO has also been used for the oxidation of 3-*n*-pentadecylphenol in ethanol and similar results are obtained as with non-immobilized MTO [83, 84]. When a nitrated analogue of the substrate is used, the results of oxidation in acetic



Scheme 4 Oxidation followed by Baeyer–Villiger rearrangement and transesterification of nitrated cardanol oil [86]

acid are completely different, yielding pentadecanoyl pentadecylphenyl esters as the major product. Probably, this is due to oxidation at the benzylic position followed by a Baeyer–Villiger rearrangement, which is known to be catalyzed by the MTO/H_2O_2 system [85], and transesterification, yielding the above-mentioned ester and nitroresorcinol (Scheme 4) [86].

3.3 Lignin and Lignin Model Compounds

Lignin is one of the three major components of lignocellulosic biomass such as trees, bushes, and grasses. Usually, it is found in 15–30% amount, dependent of the source of biomass used, the other components being cellulose and hemicellulose [87]. Lignin is a three-dimensional highly cross-linked polymer consisting of methoxylated phenylpropane monomers. In the plant structure, it is found between the cellulose and hemicellulose chains and is responsible for the sturdiness of lignocellulosic biomass. The three building blocks that make up lignin are *para*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol (Fig. 11), which are linked together in the plant via phenol radical reactions. The major challenge for using lignin as a resource for the chemical industry lies in its complex structure and polymeric nature. Therefore, most efforts in lignin research are put in the breakage of the polymeric structure to obtain simple aromatic building blocks. A review by Weckhuysen and coworkers on the valorization of lignin was recently published [88].

One of the important ways to split lignin is via oxidative cleavage. Unlike stronger catalytic oxidation systems such as OsO_4 and RuO_4, for a long time, MTO was unknown for the oxidative cleavage of olefins, yet in 2000, a first example of such a reaction was reported by the group of Herrmann. Isoeugenol and *trans*-ferulic acid, which can be extracted from sawdust or agricultural waste, were used to demonstrate the possibility of oxidatively cleaving the double bond.

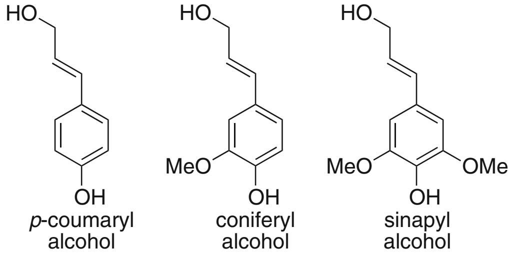
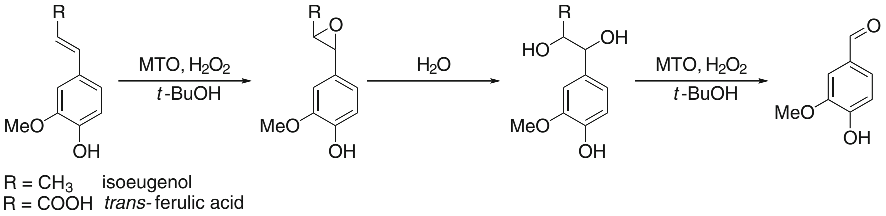


Fig. 11 The building blocks of lignin: *para*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol



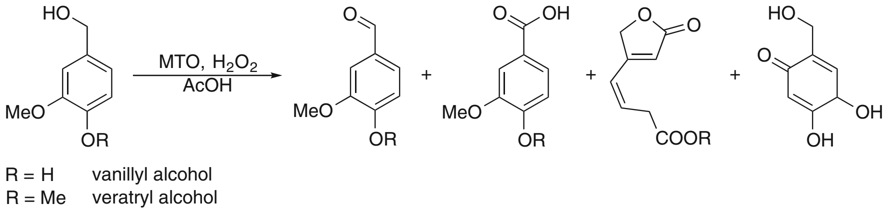
Scheme 5 MTO-catalyzed oxidative cleavage of isoeugenol and *trans*-ferulic acid to vanillin [89]

Using the MTO/H_2O_2 system in *tert*-butanol, both compounds are degraded to yield vanillin in almost quantitative yield. This oxidative cleavage is proposed to proceed via MTO-catalyzed epoxidation followed by hydrolysis of the oxirane ring and subsequent MTO-catalyzed cleavage of the diol (Scheme 5) [89].

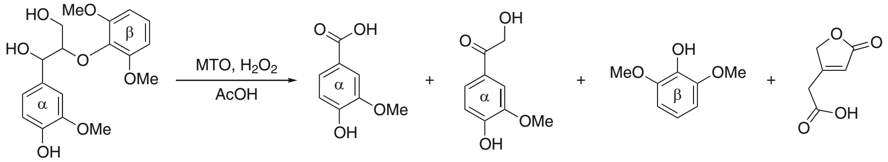
Another use of the MTO/H_2O_2 system using lignin model compounds and lignin itself was reported by the group of Saladino some years later. In glacial acetic acid as the reaction medium, various lignin model compounds, both monomeric and dimeric, and both phenolic and non-phenolic, were tested prior to switching to lignin. The simplest model compounds used were vanillyl alcohol and veratryl alcohol. With these compounds, oxidation of the benzylic alcohol to the aldehydes vanillin or 3,4-dimethoxybenzaldehyde occurs (Scheme 6), as well as oxidation to the corresponding acids. Furthermore, mucunolactone is formed with both substrates, in addition to a *para*-benzoquinone derivative in the case of vanillyl alcohol. Although the starting compounds are consumed almost completely (>95%), very low yields (<5%) of the mentioned products are obtained, resulting in a very poor mass balance (9–12%) [90].

Next, a dimeric phenolic model compound was used as substrate, modeling the β-O-4 linker that is the predominant linkage found in both softwood and hardwood lignin, i.e., the oxygen linker between the β-carbon of the aliphatic side chain and a phenol ring [88]. Here, primarily oxidative cleavage products are formed, which resemble the products obtained with vanillyl alcohol (Scheme 7). The two benzaldehyde derivatives and the lactone originate from the α-phenyl ring, while syringol originates from the β-phenyl ring [90].

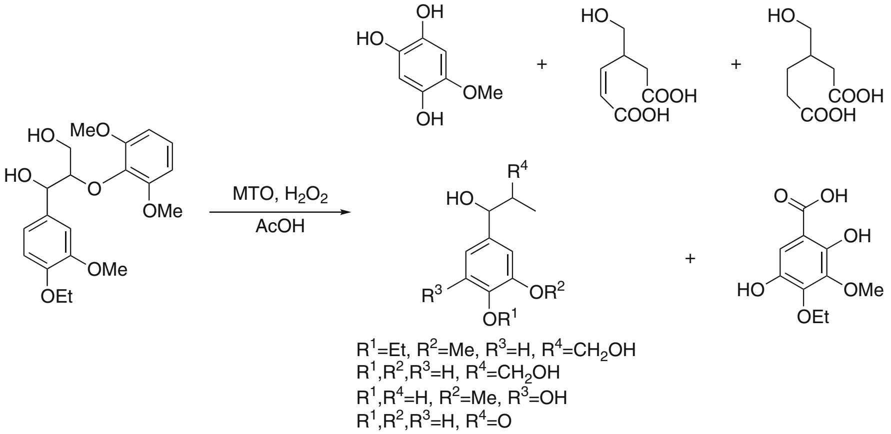
Very interesting results have been obtained with very similar model compounds, representing hardwood and softwood non-phenolic lignin. In the case of the



Scheme 6 MTO-catalyzed oxidation of vanillyl and veratryl alcohol [90]



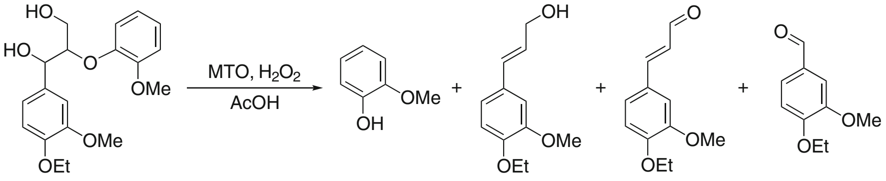
Scheme 7 MTO-catalyzed oxidation of a dilignol modeling the β-O-4 linker [90]



Scheme 8 MTO-catalyzed oxidative cleavage of a hardwood non-phenolic lignin model compound [90]

hardwood model compounds (Scheme 8), full conversion can be obtained, although non-phenolic lignin model compounds are usually less active than phenolic ones, and a wide range of products is obtained with a good mass balance (85%). The products could be formed via alkyl side-chain oxidation and cleavage of the β-O-4 linker, in some cases, followed by dealkylation of the phenolic ethers or even cleavage of the aromatic ring.

The softwood non-phenolic lignin model compound (Scheme 9) gives very different results although its structure is very similar. In this case, the major product



Scheme 9 MTO-catalyzed oxidative cleavage of softwood non-phenolic lignin model compound [90]

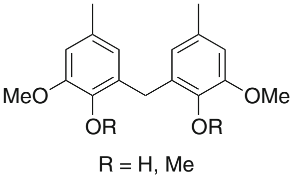


Fig. 12 Model compounds mimicking the α-1 or diphenylmethane linker

is guaiacol, with minor amounts of ethylated coniferyl alcohol and the corresponding aldehyde as well as ethylated vanillin.

Finally, two model compounds mimicking the α-1 (diphenylmethane) lignin linker (Fig. 12) were also tested for their behavior in the MTO-catalyzed oxidative cleavage reaction. Using the same conditions as above, this phenolic model compound shows some oxidation of the methyl group and some cleavage products, but again, a very low mass balance was achieved in the product analysis (11%). The non-phenolic compound mainly gives oxidation of the methyl groups to an acid and an aldehyde, while only traces of cleavage products are formed.

From these results, it is clear that the MTO/H_2O_2 system in acetic acid is not capable of cleaving the α-1 linker in an adequate manner but is very useful for the cleavage of the β-O-4 linker, which is abundantly present in most forms of lignin. Therefore, the MTO-catalyzed oxidation of three processed lignin samples was performed. The first is organosolv hardwood lignin (OSL), which is the fraction of lignin that is extracted from crushed plant material with various organic solvents. The second type is sugar cane hydrolysis lignin (SCL), and the third type is red spruce kraft lignin (RSL), a lignin type that is treated with sodium hydroxide and sodium sulfide at elevated temperature to partially degrade the lignin [88].

To clearly distinguish between acidolytic processes caused by acetic acid and catalytic processes caused by MTO, a control experiment was performed in acetic acid without catalyst and oxidant present. Comparison of the two experiments shows the effect of the MTO/H_2O_2 treatment in that a clear decrease in aliphatic hydroxyl groups occurs for all types of lignin, as well as a decrease in syringyl and guaiacyl hydroxyl groups. Only the amount of *para*-hydroxyphenyl hydroxyl groups in SCL remains about the same after the treatment. In all three cases, the amount of carboxylic acid groups also increases significantly. These data show that the MTO-catalyzed oxidative treatment of lignin is a promising process for the catalytic degradation of lignin [90].

After these first findings of the MTO-catalyzed oxidative degradation of lignin, the group of Saladino reported a year later on the treatment of lignin with immobilized MTO catalyst, using either MTO encapsulated in PS or coordinated to PVP or its oxide (PVPN). Again, the same model compounds were tested, followed by tests on processed lignin. In general the immobilized MTO shows similar conversions in converting the smaller model compounds such as vanillyl alcohol and veratryl alcohol (especially with MTO/PVP-25%) and roughly the same product distribution but a better mass balance than with non-immobilized MTO. In the case of the β-O-4 model compound, the conversions are comparable and the mass balance is somewhat better with the immobilized catalysts. Furthermore, an increased preference for the smaller guaiacol product is observed for all immobilized catalysts. When using the softwood non-phenolic β-O-4 model compound, all of the immobilized catalysts perform less than non-immobilized MTO. In addition, the product selectivities are very different depending on the carrier material. In the case of MTO/PVP-25% and MTO/PVPN-2%, a sharp increase in the amount of ethylated vanillin was observed, while MTO/PS-2% gives very low yields of all identified products ($<2.5\%$). In the case of the two α-1 model compounds, the mass balance is not affected and also the formed products are similar, yet only with the phenolic compound, using the MTO/PVPN-2% catalyst, a significant increase in the amount of formed alkyl oxidation product occurs.

Finally, the oxidative degradation of two types of processed lignin was tested with these immobilized MTO catalysts, and in all cases, the amount of aliphatic hydroxyl groups is reduced, but by far not as much as with the non-immobilized catalyst. With some catalysts, the amount of condensed and guaiacyl hydroxyl groups is even raised instead of lowered compared to the blank experiment. Finally, the amount of carboxylic acid groups increases with most catalysts, even up to the level of non-immobilized MTO, but this increase is in some cases larger than the decrease of hydroxyl groups, so oxidation of hydroxyl groups is probably not the primary source of these acid groups [91].

3.4 Lignans

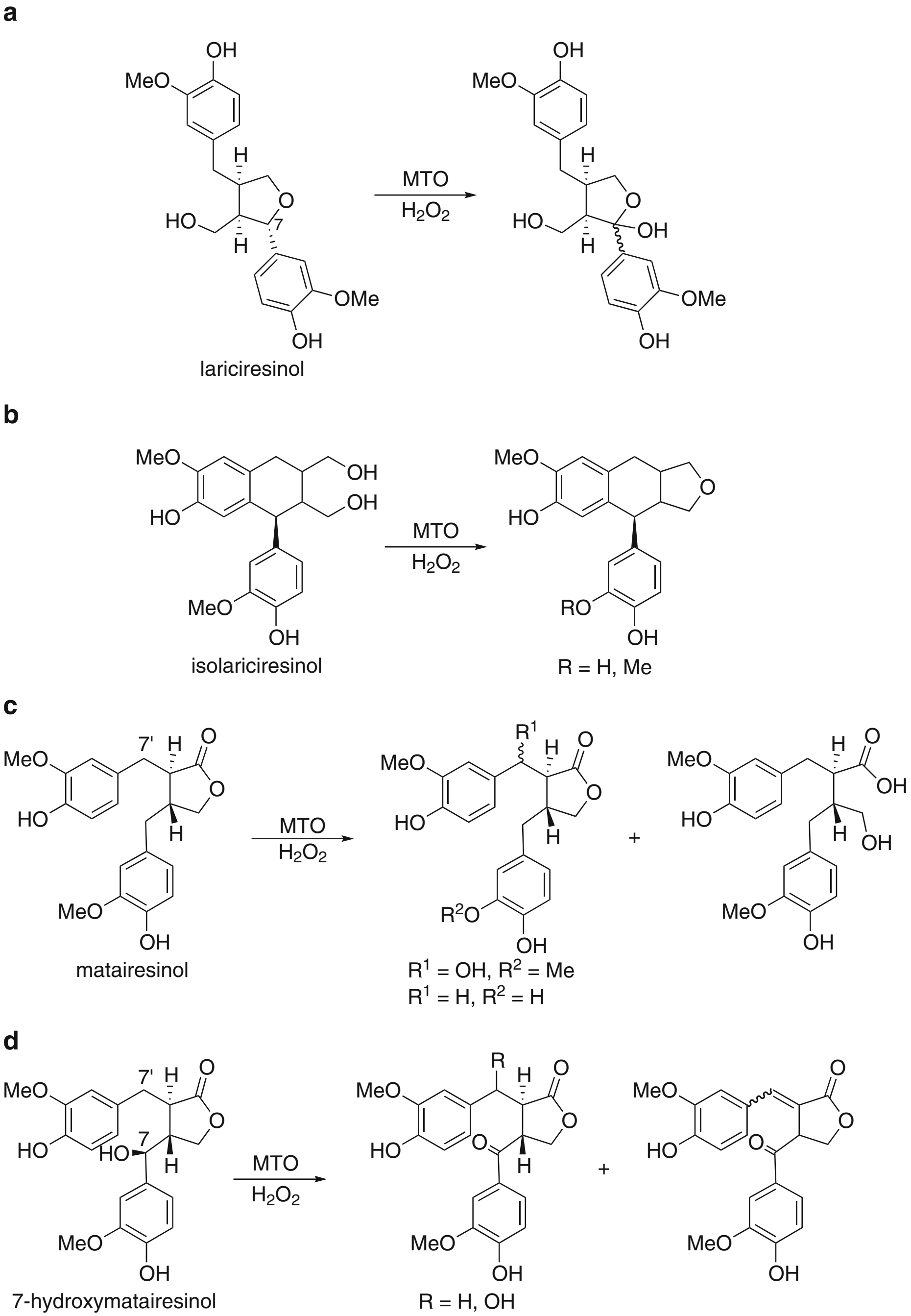
The lignans are a group of compounds found in plants and synthesized via the shikimic acid biosynthetic pathway that is also responsible for lignin synthesis [92]. These compounds are usually dimeric structures formed by a β–β linker between two phenyl propane monomers. Lignans are commonly biologically active as antioxidant, antimicrobial, antitumor, anti-inflammatory, or antiviral agents. The biological activity is tightly connected with the metabolic transformations of the lignans in the human body, of which oxidation by the cytochrome P450 enzyme family is the most important. Due to the limited amount of product formed by in vitro oxidation of lignans, an alternative oxidation process is desired to obtain these oxidized lignans in sufficient amounts [93, 94].

One of these processes is the MTO-catalyzed oxidation of lignans. A wide spectrum of lignans has been tested with this method, as shown in Scheme 10. Using the MTO/H_2O_2 system in a mixture of CH_2Cl_2 and MeCN as solvent, lariciresinol (Scheme 10a) is oxidized with 60% conversion and almost full selectivity at the benzylic 7-position. Oxidation of isolariciresinol (Scheme 10b) using the same procedure gives a mixture of two products, both resulting from ring closing of the two aliphatic hydroxyl groups to give a tetrahydrofuran moiety, in combination with the loss of one of the methyl groups on the phenol moiety in just one product. Upon treatment of the butyrolactone lignans matairesinol (Scheme 10c) and 7-hydroxymatairesinol (Scheme 10d), with the MTO/H_2O_2 system the outcome is somewhat more complicated. With the first lignan, three products are formed in roughly equal amounts, one being a demethylated species, the second being oxidized at the benzylic 7′-position, and the third one representing an oxidative ring opening of the lactone ring to result in an alcohol and an acid group. With 7-hydroxymatairesinol, four products are formed: oxidation of the hydroxyl group at the 7-position occurs first, followed by oxidation of the 7′-position, and subsequent dehydration yielding a *cis-/trans*-mixture [94].

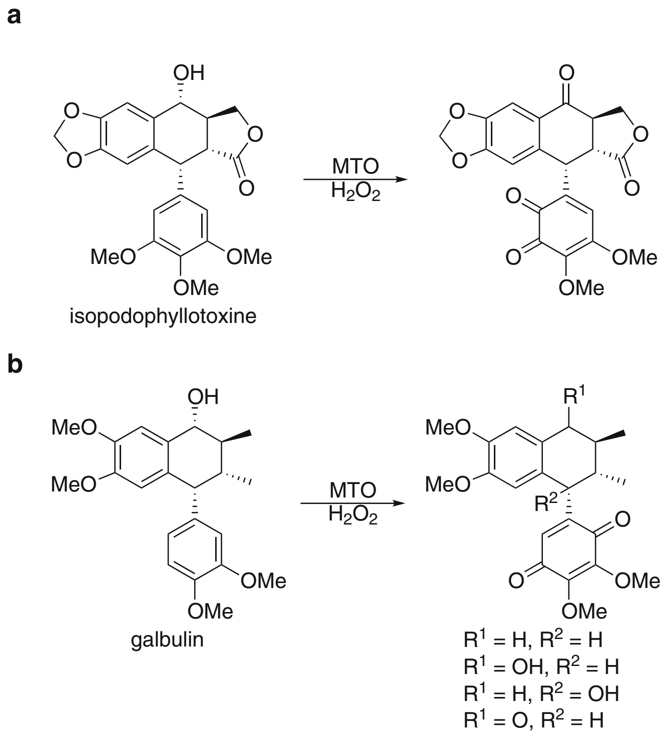
Two other lignans (isopodophyllotoxine and galbulin, Scheme 11) have been tested in various organic solvent mixtures (CH_2Cl_2/MeCN, CH_2Cl_2/EtOH or acetic acid) and with both immobilized and non-immobilized MTO.

The best result in the oxidation of isopodophyllotoxine with non-immobilized MTO is obtained in CH_2Cl_2/EtOH as the solvent at -10°C, giving full conversion after 24 h to yield a product in which both the oxidation of the alcohol group to a ketone moiety and the oxidation of the trimethoxyphenyl group to a dimethoxy-*o*-benzoquinone group has taken place in 71% selectivity. With immobilized MTO, similar results can be obtained, using MTO/PVP-2% in CH_2Cl_2/EtOH at room temperature or in acetic acid at 40°C, although a longer reaction time is needed (66 h). The other lignan, galbulin, gives a mixture of products, the major being a dimethoxy-*p*-benzoquinone species and the others being derived from oxidation at both benzylic positions to either an alcohol or a ketone group [93].

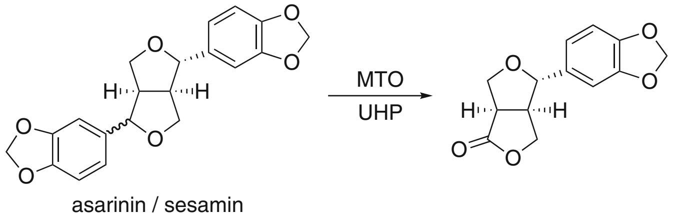
Finally, two tetrahydrofurofuran lignans (the stereoisomers asarinin and sesamin, Scheme 12) have been subjected to MTO-catalyzed oxidation. In both cases, the major product originates from oxidative cleavage of one of the phenyl-tetrahydrofuran bonds yielding a lactone. In a CH_2Cl_2/MeCN mixture using UHP as the oxidant, 65% conversion and 87% selectivity for the lactone is obtained. With immobilized MTO/PVP-2% as catalyst in CH_2Cl_2/EtOH, similar results are obtained [95].



Scheme 10 Four lignans oxidized with the MTO/H_2O_2 system: lariciresinol (**a**), isolariciresinol (**b**), matairesinol (**c**), and 7-hydroxymatairesinol (**d**)



Scheme 11 Two other lignans oxidized with MTO/H_2O_2: isopodophyllotoxine (**a**) and galbulin (**b**)



Scheme 12 Two tetrahydrofurofuran lignans asarinin and sesamin oxidized with MTO

3.5 *Other Renewables*

3.5.1 Starch

One of the most abundant biopolymers available in nature is starch. Starch is a polysaccharide consistent of glucose monomers and is found in all green plants. Next to its occurrence in food and its use in food-related industries, the major application of starch is in the paper industry, followed by the adhesives industry.

An interesting possible application in our society is in super absorbers, which are currently made with polyacrylates, but these suffer from poor biodegradability. Since the demand for short-use super absorbers is growing, a product with a short lifetime and therefore a quick and safe disposal is required. Carboxylated starch can be such a product, but first, an efficient method to oxidize starch needs to be developed. Currently used methods produce stoichiometric amounts of waste products, so the search for a catalytic process is ongoing.

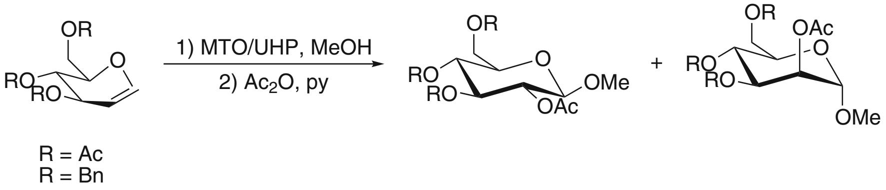
In 1999, the first oxidation of carbohydrates with MTO/H_2O_2 using HBr as additive and acetic acid as solvent was reported by the group of Herrmann. With this system, partial oxidation of the hydroxymethyl groups at the C6 position in the carbohydrate can be obtained. Only carboxylic acid groups are obtained according to ^{13}C NMR spectroscopy, and no aldehyde signals are observed. This is an interesting alternative to the stoichiometric oxidation reactions since this reaction is catalytic in all components but H_2O_2, which only gives water as a waste product [96].

The major improvement for this system lies in the replacement of the highly corrosive HBr and acetic acid by noncorrosive alternatives. In the search of an alternative bromide source, LiBr, NaBr, and KBr were tested, and the degree of oxidation, total absorbency of water (TA), and absorbency after centrifugation (CRET) are determined. Although the degree of oxidation is highest for HBr, the TA and CRET are highest with LiBr, probably caused by partial depolymerization of the starch by the acidic HBr. After optimization, a 1:1 mixture of acetic acid and water is found to give the highest TA and CRET values, thus giving the best water absorbance. When comparing the results of the optimal conditions with industrially applied processes, it is found that the MTO/H_2O_2/LiBr system in acetic acid/water is very competitive, giving somewhat lower yields but somewhat better absorption capacity. When taking the atom efficiency into account, the MTO/H_2O_2/LiBr system has an efficiency of 77% against 57% for the industrially applied TEMPO/sodium hypochlorite system, showing that this system is indeed an interesting alternative for current industrial processes as reflected in a patent application from the same authors [97, 98].

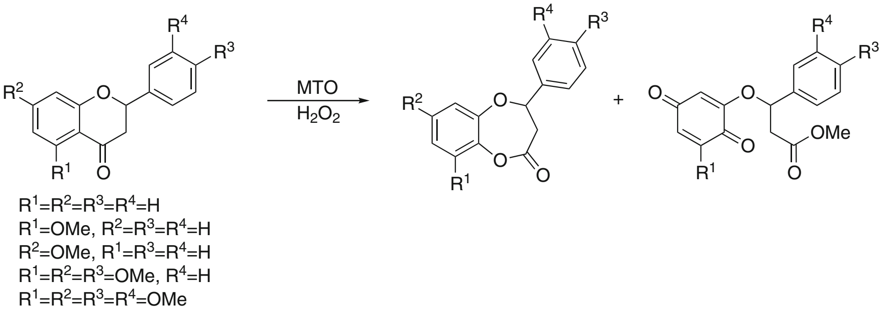
3.5.2 Glycals

Glycals have an important role as starting material in the synthesis of glycoconjugates via epoxidation and subsequent nucleophilic attack to generate the desired C-2 hydroxy glycosides. Glycoconjugates are involved in many cell–cell recognition events and are therefore connected to biological processes such as inflammation, immunoresponse, viral infections, and cancer [99]. However, the epoxidation of glycals is not trivial and is commonly performed using stoichiometric reagents. Therefore, a catalytic route is desirable and the MTO-catalyzed oxidation platform might be a good candidate.

In 2003, the first report of glycal oxidation with MTO as the catalyst and UHP as the oxidant was published by Goti and coworkers. In methanol as the solvent, triacetyl- and tribenzylglucal are epoxidized, followed by ring opening of the



Scheme 13 Oxidation of triacetyl- and tribenzylglucal to methyl glycosides [100]



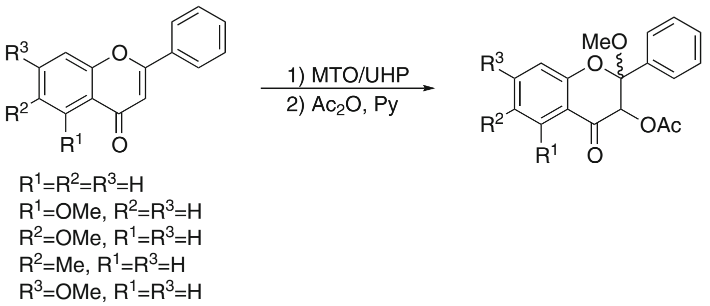
Scheme 14 Baeyer–Villiger rearrangement and oxidation of flavones with MTO/H_2O_2 [103]

epoxide ring by nucleophilic attack of the methanol. The free hydroxyl group is subsequently acetylated to obtain an α/β mixture of methyl glycosides (Scheme 13). The synthesis of glycosyl phosphates has also been described using the same principle, but with the ionic liquid [BMIM][BF_4] as solvent and dibutylphosphate as the nucleophile [100]. An immobilized MTO catalyst in methanol as well as [BMIM][BF_4] has been effectively employed in the same procedure using various acetylated and benzylated glycals as starting material [101, 102].

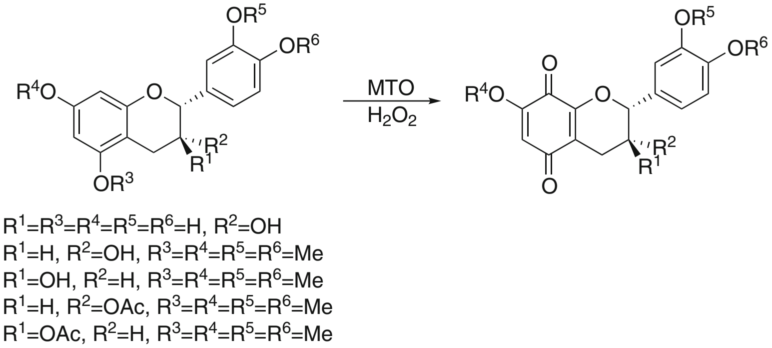
3.5.3 Flavonoids, Catechins, and Tocopherols

Flavonoids are polyphenolic compounds commonly found in some fruits, especially citrus fruits, and vegetables. They are used in the fragrancing industry and are also reported to have antiestrogenic, hypolipidemic, antihypertensive, and anti-inflammatory properties [103]. Expansion of the *O*-heterocyclic ring is not much reported in literature but could be a key step in the industrial synthesis of benzodiazepine analogues. As mentioned earlier, the MTO/H_2O_2 system is known to catalyze the Baeyer–Villiger rearrangement reaction in a catalytic fashion.

Baeyer–Villiger rearrangement of flavanone derivatives with MTO/H_2O_2 was first reported in 2001 by Saladino and coworkers and has successfully been applied for various substituted flavanones (Scheme 14). In the case where R^1, R^2, and R^3 are methoxy groups (naringenin) or when all R-groups are methoxy groups (hesperetin), oxidation toward the benzoquinone product is the major product



Scheme 15 Oxidation and subsequent acetylation of substituted flavanones with MTO/UHP [104]

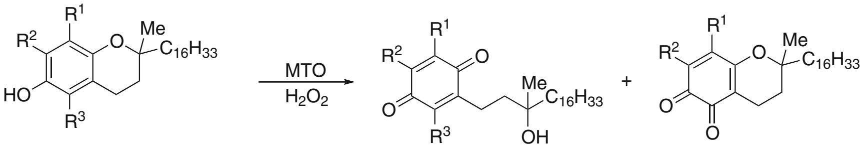


Scheme 16 MTO-catalyzed oxidation of various catechins [105]

[85]. This quinone formation can be suppressed by the use of pyridinium acetate as additive [85] or by using MTO immobilized on PVP or PVP oxide, to yield the desired seven-membered lactone ring in moderate to good yields [103].

Another type of flavones bears a double bond in the *O*-heterocyclic ring and can also be oxidatively functionalized at this bond with MTO (Scheme 15). Using the MTO/UHP system with substituted flavanone in refluxing methanol, followed by acetylation, *cis*- and *trans*-3-acetoxy-2-methoxyflavanone is obtained [104].

A class of compounds closely related to flavonoids is the catechins. Catechin is the reduced form of flavanone, where the ketone is replaced by an alcohol group. Catechins are widely found in fruits and vegetables, especially in grapes, where they are a major quality factor for the resulting wine. Catechins can be oxidized with the MTO/H_2O_2 to obtain the corresponding *para*-benzoquinones. Using various substituted catechins as substrate and MTO or its immobilized form as catalyst in most cases, full conversion is obtained and a selectivity for the *para*-benzoquinone of 20–45%. In the case of the immobilized catalyst MTO/PVP-25%, a recyclability test was performed with the second and third substrate (Scheme 16), and during five runs, full conversion is retained, while selectivity drops only slightly from 38% to 33% and from 36% to 32%, respectively [105].



α-tocopherol: R^1=R^2=R^3=Me
β-tocopherol: R^1=R^3=Me, R^2=H
γ-tocopherol: R^1=R^2=Me, R^3=H
δ-tocopherol: R^1=Me, R^2=R^3=H

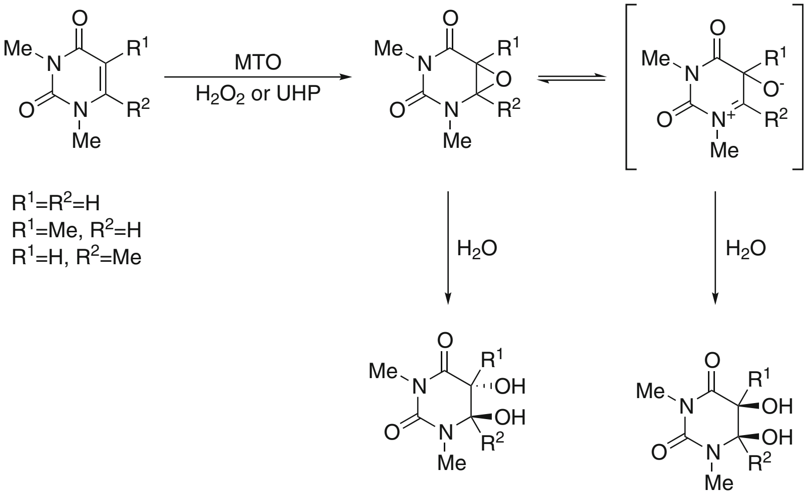
Scheme 17 MTO-catalyzed oxidation of the different tocopherols [106]

Another class of compounds that is closely related to the flavonoids and catechins is the class of the tocopherols. Four different types of tocopherols are known with different substitution patterns, as depicted in Scheme 17. Oxidation of tocopherols can also be performed with MTO/H_2O_2 in order to give benzoquinones. Oxidation of α-tocopherol with MTO/H_2O_2 in ethanol gives the *para*-benzoquinone, regardless of whether the phenol is protected with a methyl or an acetyl group or not. In contrast, the acetyl-protected α-tocopherol gives very low yields. Oxidation of either δ- or γ-tocopherol, both without substitution at the R^3 position, results in a mixture of *ortho*- and *para*-benzoquinone in roughly 1:1 ratio in most cases, where in the former product, the bicylic skeleton is still intact [106].

3.5.4 Nucleic Acids and DNA

Oxidative transformations of nucleic acids have been extensively studied in the past because of the possibility of DNA strand scission. These studies have included the testing of MTO as a catalyst for the oxidation of the nucleic acids uracil and adenine as reported by Saladino and coworkers [107]. The oxidation of uracil yields three possible products, the epoxide and two hydrolysis products, the *cis*-product via direct hydrolysis, and the *trans*-product via hydrolysis of the mesomer of the epoxide (Scheme 18). Depending on the employed reaction conditions, various amounts of the different products are formed. Using MTO/H_2O_2, the major product obtained from non-substituted uracil is the epoxide with some *trans*-diol. The hydrolysis process is strongly suppressed when UHP is used as the oxidant. For the methyl-substituted uracils as substrate and H_2O_2 as the oxidant, the major product is the *trans*-diol with some *cis*-diol. Use of UHP as the oxidant again shifts the preference toward the epoxide, with minor amounts of *trans*-diol as side product. Good to excellent conversions are obtained for various adenine derivatives in combination with H_2O_2 to yield the *N*-oxide as the major product.

As an example of MTO-mediated DNA transformation, the effect of oxidation on plasmid pBG1 has been tested. When no MTO is present, minor amounts of DNA cleavage occurs, but at increasing concentrations of MTO up to 100 μM, the amount of DNA cleavage increases up to almost 30% [107].



Scheme 18 MTO-catalyzed oxidation of uracil derivatives [107]

3.5.5 Amino Acids

The synthesis of unnatural amino acids and peptides is of great interest since it offers the possibility to design new biologically active protein analogues. One of the possible interesting transformations is side chain oxidation of amino acids, for which MTO can be used. It is reported that various *N*-Boc protected amino acids such as methionine (Met), cysteine (Cys), and tryptophan (Trp) can be oxidized with the MTO/H_2O_2 system [108].

The sulfur-containing side chain of Met can be oxidized with this system to the corresponding sulfone using 2 equivalents of H_2O_2 in ethanol, although in acetic acid, better yields are obtained. The side chain of Cys is oxidized in ethanol to obtain a sulfoxide–sulfide-bridged dimer with minor amounts of sulfone and sulfinic ester. Switching the solvent to acetic acid yields the sulfone as the major product. Oxidation of Trp can also be performed in ethanol and acetic acid, and in both cases, oxidation to the corresponding amide occurs.

Similar oxidation products are formed when small peptides, containing Met or Trp, are treated with the MTO/H_2O_2 system, irrespective of the position of the amino acid that is oxidized in the peptide. A combination of Met and Trp in the peptide Boc-Met-Trp-OMe approximately gives a 1:1 mixture of products, one oxidized at the Met side chain to give a sulfoxide, and the other bearing both a sulfoxide and an amide. When only 1 equivalent of oxidant is used, the former becomes the dominant product with only minor amounts of the latter product. The fact that only sulfoxide is formed and no sulfone could be an indication that once the sulfoxide is formed, the steric hindrance caused by the Trp side chain prevents the second oxidation. This is also illustrated by the oxidation of Cbz-Trp-Met-OMe, where the Met is quantitatively converted to the sulfoxide without oxidation of the tryptophan [108].

4 Deoxygenation of Renewables with Organometallic Rhenium Complexes

The use of organometallic rhenium complexes has found a very broad scope as oxidation catalysts as described in the previous section, making MTO the catalyst of choice for many oxidation reactions of olefins. Interestingly, MTO and related rhenium compounds have also found application in the reverse reaction, the deoxygenation of alcohols and diols. Especially in recent years, this reaction has attracted much attention due to the increased interest in the use of biomass as feedstock for the chemical industry. This section provides an overview of the use of rhenium-based catalysts in the deoxygenation reaction of renewables.

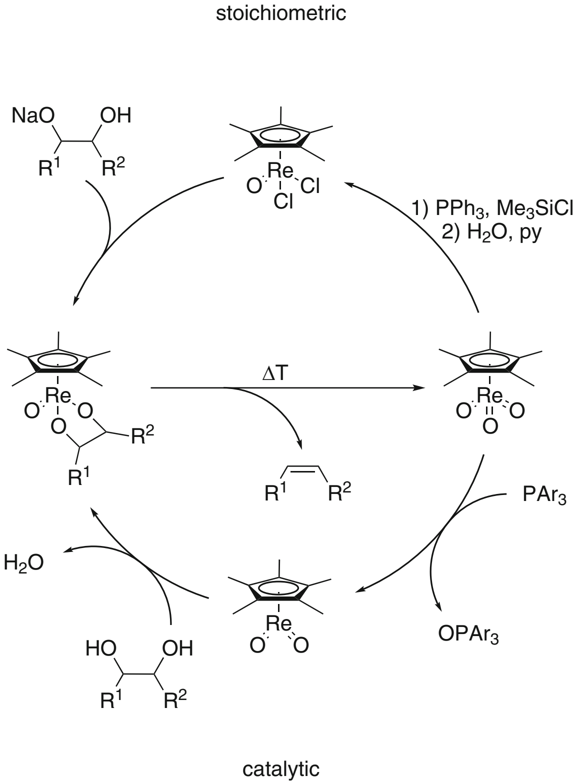
Due to the explosive growth of the amount of biomass-related research in recent years [109], also the interest in the deoxygenation of biomass has increased rapidly. The importance of deoxygenation of biomass lies inherently in the nature of biomass. As previously described, lignocellulosic biomass mostly consists of cellulose and hemicellulose, both carbohydrates, and lignin. Carbohydrates have an oxygen-to-carbon (O:C) ratio of 1, while the oil-based chemicals that the chemical industry currently uses have a very low O:C ratio. In order to obtain high-value chemicals which the chemical industry can incorporate in current processes and facilities, it is thus needed to decrease the O:C ratio. One of the important ways to do this is via deoxygenation reactions [110, 111].

4.1 Deoxydehydration of Diols and Polyols

After the discovery of MTO as a very potent oxidation catalyst in 1991 [3], many research efforts have been devoted to understanding the mechanism of this reaction and to the synthesis and isolation of possible intermediates. As part of these efforts, a number of (pentamethylcyclopentadienyl) oxorhenium(V) diolates (Cp*ReO (diolate)) were synthesized and characterized by the groups of Herrmann [112, 113] and Gable [114–116] as possible intermediates in the oxidation chemistry of rhenium. Interestingly, these rhenium(V) diolate complexes all expel an olefin to obtain the corresponding Cp*ReO_3 complex upon heating (Scheme 19, left to right). Cp*ReO_3 was previously found to be a very poor catalyst for the oxidation reaction, but these reports gave a lead toward the use of Cp*ReO_3 as a deoxydehydration catalyst. An important next step was made in 1994 by Gable with a report on the synthesis of Cp*ReO(diolate) complexes from Cp*ReO_3 with triphenylphosphine as reducing agent in the presence of *para*-toluenesulfonic acid (pTSA) and molecular sieves in tetrahydrofuran (Scheme 19, right to top to left) [117].

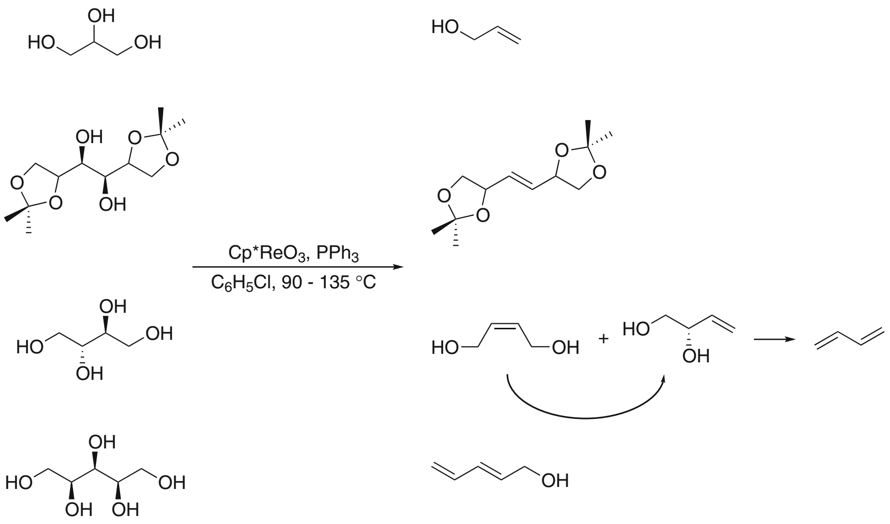
By combining the methods reported above, Cook and Andrews in 1996 discovered the first catalytic process based on the stoichiometric reactions with rhenium (V) diolate complexes reported in the 10 years before. The use of a reductant in the form of a triarylphosphine was found to be critical to close the deoxydehydration

Scheme 19 Stoichiometric (*top*) and catalytic (*bottom*) reactions of Cp*ReO$_3$ with diols



catalytic cycle from diol to alkene. It was shown that by using 2 mol% Cp*ReO$_3$ and 1.2 equivalent of triphenylphosphine in chlorobenzene at 90°C phenyl-1, 2-ethanediol can be deoxydehydrated to form styrene in a quantitative manner. The authors proposed a mechanism where the phosphine reduces the Cp*ReO$_3$ catalyst to a rhenium(V) intermediate, which reacts with the diol and subsequently expels the olefin to regenerate Cp*ReO$_3$, as schematically shown in the bottom half of Scheme 19. The major problem in this reaction is the overreduction of the rhenium(V) species to a rhenium(III) species leading to deactivation of the catalyst. Two solutions to this problem are described, on the one hand, the use of a less active reductant in the form of tris(perfluorophenyl)phosphine to diminish overreduction and, on the other hand, the use of pTSA to accelerate the rate of formation of the rhenium diolate intermediate [118].

This system has also been applied to deoxydehydrate suitable substrates from renewables. Glycerol is cleanly deoxydehydrated to give allyl alcohol using Cp*ReO$_3$, PPh$_3$ and chlorobenzene in biphasic conditions at 125°C (Scheme 20). When *N*-methyl-2-pyrrolidinone (NMP) is used as the solvent a homogeneous system is created, but this leads to rapid catalyst deactivation and only 42% yield of allyl alcohol. The protected alditol 1,2:5,6-diisopropylidene-D-mannitol reacts smoothly in chlorobenzene with this system, yielding the corresponding *trans*-

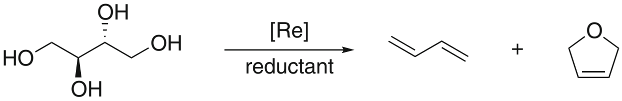


Scheme 20 Deoxygenation of renewables with Cp*ReO$_3$ as catalyst and PPh$_3$ as reductant

alkene in 86% yield. When the unprotected alditol erythritol is used as substrate at 135°C in this reaction, both 3-butene-1,2-diol, and 2-butene-1,4-diol are observed in a 85:15 ratio, but the major product is completely deoxygenated 1,3-butadiene in 80% yield (Table 5, entry 1). It is found that the 1,4-diol isomerizes to 1,2-diol under the applied reaction conditions, which means that intermediate formation of 1,4-diol is not detrimental for the overall yield of butadiene. Finally, xylitol was used as substrate to yield 2,4-pentadiene-1-ol as the reaction product (no yield is reported) [118].

After this initial report of deoxydehydration using rhenium complexes, it took almost 15 years before further research has been reported into this subject. In 2009, a report by the group of Abu-Omar marked the start of renewed interest in the area. In this report, the major problems of the method of Cook and Andrews are dealt with. First of all, the phosphine, which causes overreduction and creates stoichiometric amounts of phosphine oxide waste, is replaced by hydrogen gas, which only produces water as waste. Furthermore, the catalyst in this report is MTO, which is readily available in large quantities, and the substrate scope is expanded to epoxides. 1,2-Epoxyhexane, for instance, is deoxygenated to obtain hexane in 96% yield after 8 h at 150°C under 21 bar of hydrogen pressure. When the pressure is reduced to 5.5 bar, 1-hexene is the major product in 95% yield. 1,2-Hexanediol is also tested as substrate under these conditions, but much lower yields are obtained (respectively 50% 1-hexene at 21 bar and 18% 1-hexene at 5.5 bar). Several renewables are used as substrate with this system: 1,4-anhydroerythritol, obtained from acid-catalyzed ring closing of erythritol, is deoxydehydrated to the 2,5-dihydrofuran in 25% yield and tetrahydrofuran in 5% yield, using 34.5 bar of hydrogen pressure. However, when erythritol itself is used as substrate under identical conditions, only significant charring occurs (Table 5, entry 2).

Table 5 Rhenium-catalyzed deoxygenation of erythritol to 1,3-butadiene and 2,5-dihydrofuran



Entry	Catalyst	Red.	*T* (°C)	*t* (h)	1,3-Butadiene yield (%)	2,5-Dihydrofuran yield (%)	Reference
1	Cp*ReO_3	PPh_3	135	28	80	–	[118]
2	CH_3ReO_3	H_2 (34.5 bar)	150	8	–	–	[119]
3	CH_3ReO_3	Na_2SO_3	150–160	100	14	2	[121]
4	NBu_4ReO_4	Na_2SO_3	150–160	100	27	6	[121]
5	$Re_2(CO)_{10}$	3-Octanol[a]	160	12	–	62	[122]

[a] *para*-Toluenesulfonic acid added

A similar mechanism as the one of Cook and Andrews is proposed by the authors for the reactions, where a methyldioxorhenium(V) species is generated followed by reaction with the substrate, being either a diol or an epoxide. Next, however, the diolate is converted to an epoxide–rhenium adduct, which is subsequently expelled via a metallaoxetane [119].

Shortly hereafter, the group of Nicholas reported a very similar system, again using MTO as the catalyst and sulfite as the reducing agent. With this system in benzene at 150°C, phenyl-1,2-ethanediol is deoxydehydrated to form styrene in 44% yield at 90% conversion after 40 h of reaction time. When styrene oxide is used as substrate, 40% styrene at 75% conversion is obtained after 30 h of reaction time. Switching to aliphatic alcohols requires longer reaction times for high conversions to be obtained [120]. A year later, the same system was expanded in its scope toward biomass-derived polyols such as erythritol. Heating a mixture of *meso*-erythritol, NBu_4ReO_4 and sodium sulfite in benzene for several days at 150–160°C results in the formation of 1,3-butadiene (27% yield), 2,5-dihydrofuran (6% yield), and *cis*-2-butene-1,4-diol (3% yield) at a conversion of 44% (Table 5, entry 3). When MTO is used as the catalyst, again substantial charring is observed, and much lower yields are obtained (respectively 14%, 2%, and 5%, entry 4). Various additives such as nitrogen bases were explored as well as various reductants, either sulfites, phosphines, or alcohols, but the initial reaction conditions give the best results [121].

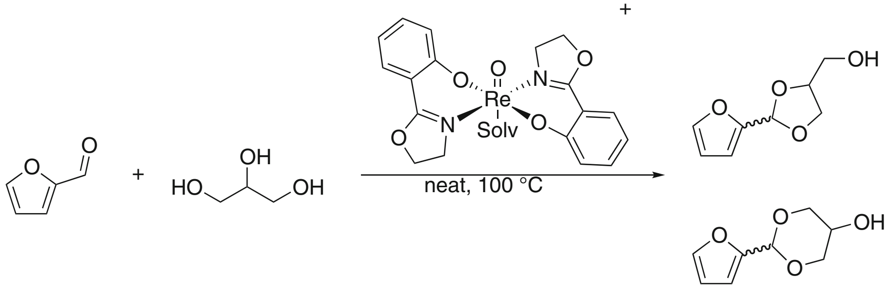
The other report in the area comes from the groups of Bergman and Ellman, who have reported on the use of decacarbonyldirhenium ($Re_2(CO)_{10}$) as catalyst for the deoxydehydration of diols. Using this rhenium(0) catalyst at 180°C, 4,5-octanediol is disproportionated into 4-octene and 4,5-octadione, giving a yield of 50% for the olefin. When adding a simple alcohol such as 5-nonanol or 3-octanol, and using 1,2-tetradecanediol as the substrate, 1-tetradecene is formed in 83% yield, and the alcohol is oxidized to the corresponding ketone. Upon addition of pTSA or sulfuric acid, the temperature can be reduced to 155°C while still yielding the alkene in good yield. In the presence of pTSA and 3-octanol at 160°C, this system is able to transform erythritol into 2,5-dihydrofuran in 62% yield (Table 5, entry 5). Probably, the acid causes the cyclization of the polyol to 1,4-anhydroerythritol, followed by the deoxydehydration to obtain 2,5-dihydrofuran. Interestingly, neither of these reactions give any product in the absence of air, thus indicating that oxygen plays a role in the reaction mechanism [122].

4.2 Dehydration of Alcohols

Where rhenium-catalyzed deoxydehydration has attracted a lot of interest, only two reports concerning dehydration catalyzed by rhenium complexes are noteworthy in view of their application on biomass-derived substrates. The first was published in 1996 by Zhu and Espenson and uses MTO as catalyst for the dehydration reaction of various alcohols, either aliphatic or aromatic, to obtain the corresponding olefins. Using MTO in benzene or in the alcohol itself at room temperature after 3 days gives reasonable turnovers and, in the case of benzylic alcohols, good yields. In the same paper, MTO is used for the amination, etherification, and disproportionation of alcohols, which are all reactions interesting in the viewpoint of biomass transformation [123].

The other report is more recent and elaborates on the report of Espenson. Here, various rhenium catalysts were tested in the dehydration reaction of benzylic alcohols in toluene at 100°C. It was found that high-valent rhenium species perform better than low-valent rhenium, with rhenium(VII) oxide as the most active catalyst, followed by MTO and the rhenium(V) complex $ReIO_2(PPh_3)_2$. Using rhenium (VII) oxide, various benzylic alcohols are dehydrated to the corresponding styrenes, and the reaction characteristics are compared to the benchmark catalyst sulfuric acid. It was found that rhenium(VII) oxide is more active than sulfuric acid, while the selectivity is comparable or better. Most interesting for the application on biomass is the observation that methoxy-substituted 1-phenylethanol is very rapidly dehydrated using this system, which opens up possibilities for the use on lignin-derived substrates [124].

One recent publication from the group of Abu-Omar reports on a condensation reaction involving glycerol and furfural, both renewables, to produce dioxolanes, formally a dehydration reaction. Here, a cationic oxorhenium(V) oxazoline species is used as the catalyst for the formation of various 1,3-dioxalanes from furfural with diols or epoxides under mild conditions (Scheme 21). Especially interesting is the reaction of furfural with glycerol to obtain a 70:30 mixture of the corresponding 1,3-dioxolane and 1,3-dioxane in solvent-free conditions [125].



Scheme 21 Rhenium-catalyzed condensation reaction of furfural with glycerol to obtain the corresponding 1,3-dioxolane and 1,3-dioxane

5 Concluding Remarks

This chapter provides an overview of how the relatively young field of rhenium-based homogeneous catalysis has drawn much interest in various transformations of biomass-derived chemicals in the last 20 years. Although many reports highlight the activity of rhenium complexes, in particular MTO, in oxidative transformations of bio-based substrates such as oils and terpenes, only in recent years have researchers begun to investigate the use of rhenium catalysts in deoxygenation reactions. The successful development of such catalysts would allow for the conversion of biomass feedstocks into products with a low O:C ratio, which the chemical industry has already been using for decades. Synthetic procedures based on these catalytic reactions may be able to provide alternative pathways to access some of the genuine chemicals that are of interest for both the bulk and fine chemical industry, based on biomass starting feeds. Combined with the increasing pressure on the availability and cost of fossil feedstock, it is our belief that this field is looking at a flourishing future.

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Recent Developments in Catalytic Activation of Renewable Resources for Polymer Synthesis

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Abstract This review describes the application of organometallic and inorganic complexes as initiators and catalysts for polymerizations using renewable resources. It focuses on the ring-opening polymerization of lactide and the alternating copolymerization of carbon dioxide and epoxides. For lactide ring-opening polymerization, a general background to the reaction mechanism, kinetics, stereochemical control and polymerization control is presented. This is followed by reviews of the use of groups 3 and 13 complexes as initiators. Group 3 complexes show excellent rates, amongst the fastest reported for this polymerization, and in some cases stereocontrol. The group 13 complexes have good precedent for stereocontrol; recent advances using heavier group 13 elements, In and Ga, are highlighted. For the alternating copolymerization, an overview of the reaction kinetics, mechanism and control is presented. Recent advances in the use of catalyst operating at low pressure and dinuclear catalysts are presented.

Keywords Carbon dioxide and epoxides copolymerization • Group 13 metal catalysts • Group 3 metal catalysts • Lactide polymerization • Polycarbonate • Polylactide

Contents

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Abbreviations

[PPN]Cl	*Bis*(triphenylphosphoranylidene)ammonium chloride
BDI	β-Diiminate
CHC	Cyclohexene carbonate
CHO	Cyclohexene oxide
DMAP	4-Dimethylaminopyridine
DNP	2,4-Dinitrophenolate
FT-IR	Fourier transform infrared
GPC	Gel permeation chromatography
MALDI-ToF	Matrix-assisted laser desorption ionization – time of flight (detection)
N-MeIm	*N*-Methylimidazole
PCHC	Poly(cyclohexene carbonate)
PDI	Polydispersity index
PO	Propylene oxide
PPC	Poly(propylene carbonate)
P_s	Probability of forming a new syndio-dyad
P_i	Probability of isotactic diad formation
rac-LA	*rac*-Lactide
T_g	Glass transition temperature
TOF	Turnover frequency
TON	Turnover number
TPP	Tetraphenylporphyrin

1 Introduction

The production of polymers from renewable resources is attracting considerable attention, both from academic and industrial research interests. Currently, polymers are produced on an approximately 150 million ton scale per year and are mostly derived from petrochemicals, with approximately 7–8% of worldwide reserves being consumed each year [1]. Concerns regarding the long-term sustainability of such petrochemical feedstocks, coupled with increasing and fluctuating prices, environmental pollution and problems with security of supply, have driven research into alternative means to produce polymers.

Biomass (plant matter) has been extensively investigated as a raw material for polymer production. Historically, plants are well-known sources for polymer fibres, most notably cotton, linen, jute, hemp, etc. Cellulose, and its derivatives, and phenolic resins (derived from lignin) are commercial products and have been extensively investigated [2–8]. Another promising type of bio-derived polymers is the poly(hydroxyl alkanoates), which can be produced from bacteria, via condensation polymerization or even by ring-opening polymerization of lactones [9–14]. The application of high-oil-content plants, and naturally occurring fatty acids, in polymer synthesis has also been a long-standing research field and has been recently reviewed [15, 16]. The focus of this review will be on the ring-opening polymerization of lactide, from lactic acid produced by the fermentation of D-glucose. For detailed explanations of the properties of polylactide (PLA), the reader is referred to other reviews [17]. We focus particularly on efficient routes to prepare PLA because its synthesis presents some interesting opportunities and future challenges for organometallic and inorganic chemistry. The theme of this review is to understand the polymerization reaction and, in particular, to compare initiators (catalysts) and mechanisms.

Carbon dioxide is an attractive renewable resource being of low toxicity, abundant and the waste product of many processes. There is precedent, dating back to 1969, for the copolymerization of CO_2 and strained heterocycles, most notably epoxides [18]. The focus on this review will be on understanding the polymerization catalysts for the alternating copolymerization.

2 Lactide Ring-Opening Polymerization

2.1 Introduction

Polylactide is a degradable polyester, formed by the ring-opening polymerization of lactide or the condensation polymerization of lactic acid. Lactide is produced from lactic acid, which derives from the fermentation of D-glucose, which is usually harvested from high-starch-content crops, such as corn or sugar beet (Fig. 1).

The most effective, and commercially applied, method to produce polylactide is via the ring-opening polymerization of lactide. This process is initiated by metal complexes and proposed to occur via a coordination–insertion mechanism, as illustrated in Fig. 2. The most common initiators for this polymerization are Lewis acidic metal alkoxide or amide complexes. Key initiator criteria are sufficient Lewis acidity to enable binding and activation of the lactide unit and a labile metal alkoxide (or amide) bond so as to enable efficient insertion.

The putative mechanism involves coordination and activation of the lactide by the metal complex (1, Fig. 2). The lactide, once activated, is subsequently attacked by the metal alkoxide group (another way to view this is that lactide inserts into the metal alkoxide bond) (2, Fig. 2). The putative intermediate then undergoes ring opening of the lactide, by an acyl bond cleavage, and a new metal alkoxide bond is

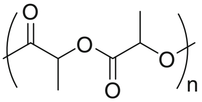


Fig. 1 Polylactide

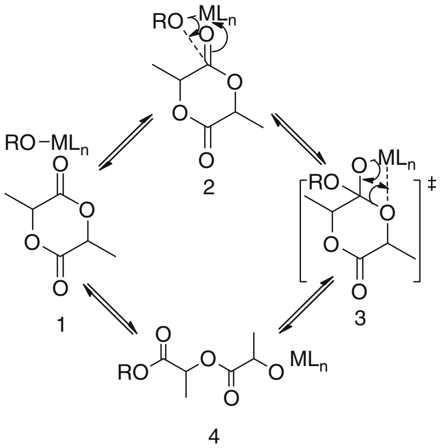


Fig. 2 Coordination– insertion mechanism; *M* metal, *OR* alkoxide group, L_n ligand(s)

formed (3 and 4, Fig. 2). This sequence is subsequently repeated in order to produce a growing polymer chain. The growing chain end is end-capped with an ester (initiation from an alkoxide) or amide (initiation from an amido) functionality; the other end of the chain is a hydroxyl group after hydrolysis of the O–M bond (during polymer workup). The reaction is thermodynamically favourable at room temperature ($\Delta H = 22.1$ kJ/mol for 1 M solution of *SS*-lactide) due to the relief of the lactide ring strain [19–21].

A wide range of metal complexes have precedent for this catalysis, including main group elements, such as Sn(II), Al(III); transition metals, including Zn(II), Ti (IV), Zr(IV), Y(III), Fe(II) and others; and lanthanides and alkali/alkaline earth elements, including Li, Mg and Ca. The selection of the metal complex (initiator) is very important as it controls the rate, the economics (via the cost and loading of complex which must be used) and the properties of the resulting polymer. A number of factors need to be considered when comparing and selecting metal complexes for this catalysis; these will be outlined.

2.1.1 Polymerization Rate

Understanding the polymerization kinetics is of fundamental importance not only for comparing different initiators but also understanding the catalytic cycle and preparing more active compounds. The polymerization generally obeys a second-order rate law, with first-order dependencies on both monomer (lactide) and

Table 1 Descriptions of polymerization rates based on a 1 M [LA] and 1 mol% [I] system

Timescale	Description
<1 min	Very fast/rapid
<1 h	Fast
<1 day	Good
1 day to 1 week	Moderate/slow

initiator concentrations (occasionally higher orders in initiator are observed, particularly where aggregation occurs) [22, 23]:

$$-\frac{\mathrm{d}[\mathrm{LA}]}{\mathrm{d}t} = k_{\mathrm{p}}[\mathrm{LA}]_0[\mathrm{I}]_0,$$

where k_{p} = propagation rate constant, $[\mathrm{LA}]_0$ = initial lactide concentration and $[\mathrm{I}]_0$ = initial concentration of the initiator.

In order to determine k_{p} and also for the purposes of comparing initiators (tested under the same monomer concentrations and experimental conditions), this rate expression can be reduced to a pseudo-first-order equation:

$$-\frac{\mathrm{d}[\mathrm{LA}]}{\mathrm{d}t} = k_{\mathrm{obs}}[\mathrm{LA}]_0,$$

where k_{obs} = pseudo-first-order rate constant.

Although the best method to compare initiator activities is via the determination of k_{p}, the values of k_{obs} can also provide useful data on catalysts' activities, particularly if a common set of conditions are applied. In some cases, no rate data is available; rather, a time at a particular monomer conversion is reported. In order to discuss polymerization rates in this review, we have attempted to compare experiments run under standard conditions. It seems common in this field to run polymerizations at a lactide concentration of 1 M and an initiator concentration of 10 mM (1 mol%); under such conditions, initiators can be ranked according to how long they take to reach >90% conversion, as illustrated in Table 1.

2.1.2 Polymerization Control

Controlled polymerization occurs when the rate of initiation is faster than the rate of propagation and when there are limited chain transfer or chain termination reactions. Lactide ring-opening polymerization is not a living polymerization as there are chain transfer reactions, most notably transesterification reactions; usually, these are kinetically controlled. Experimental criteria which should be fulfilled to apply the term controlled polymerization include a linear evolution of the PLA M_{n} with lactide conversion; a linear increase in PLA M_{n} with lactide/initiator (at constant lactide concentration); PLA of narrow polydispersity; a higher rate of propagation than chain transfer; a higher rate of propagation than chain termination;

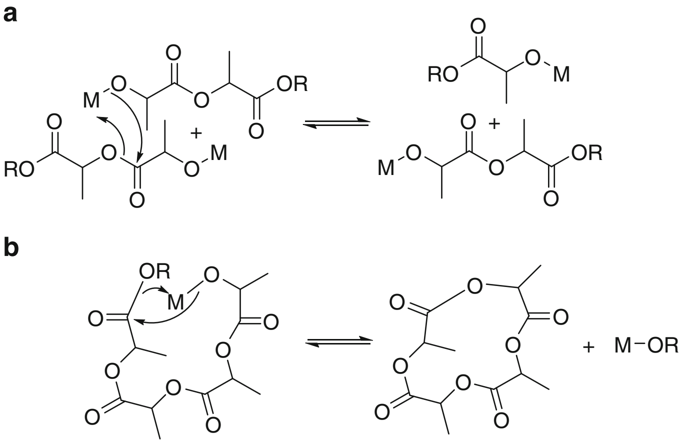


Fig. 3 (**a**) Intermolecular transesterification; (**b**) intramolecular transesterification

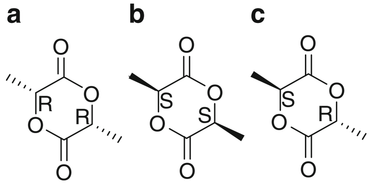


Fig. 4 (**a**) *RR*-lactide; (**b**) *SS*-lactide; (**c**) *meso*-lactide

and the ability to initiate further polymerization from active chain ends – i.e. formation of block copolymers and control over the chain end groups. The metal initiator influences the polymerization control. In certain circumstances, for example, the production of block copolymers, the application of initiators exerting a high degree of polymerization control would be necessary.

The major side reactions in lactide ROP are intramolecular and intermolecular transesterification (Fig. 3). Intramolecular transesterification leads to formation of mixtures of linear and cyclic polymers, ultimately reducing the molecular weight of the polymer sample. Intermolecular transesterification, or chain transfer, leads to a broadening of the polymer molecular weight distribution. The extent of these processes can be experimentally verified using mass spectrometry, most commonly using ESI or MALDI-ToF mass spectrometry and by $^{13}C\{^1H\}$ NMR spectroscopy [24, 25].

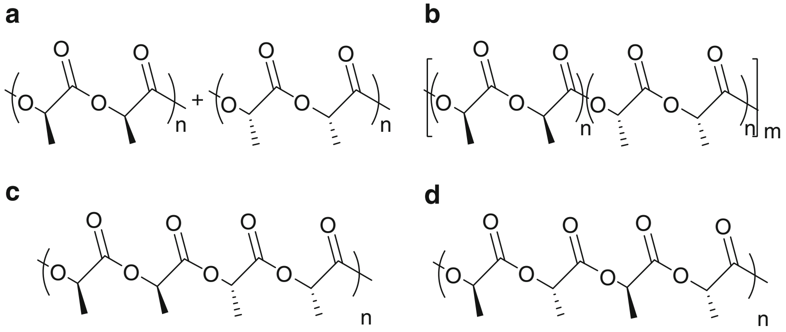


Fig. 5 (**a**) Stereocomplex PLA; (**b**) stereoblock PLA; (**c**) heterotactic PLA; (**d**) syndiotactic PLA

2.1.3 Stereocontrol

There are three stereoisomers of lactide: *meso*-[*R*,*S*(D,L)], *RR*(D)- and *SS*(L)-lactide (Fig. 4). The 50:50 mixture of the *RR*- and *SS*-enantiomers is known as *rac*-lactide.

The tacticity of PLA influences the physical properties of the polymer, including the degree of crystallinity which impacts both thermo-mechanical performance and degradation properties. Heterotactic PLA is amorphous, whereas isotactic PLA (poly(*RR*-lactide) or poly(*SS*-lactide)) is crystalline with a melting point of 170–180°C [26]. The co-crystallization of poly(*RR*-lactide) and poly(*SS*-lactide) results in the formation of a stereocomplex of PLA, which actually shows an elevated, and highly desirable, melting point at 220–230°C. Another interesting possibility is the formation of stereoblock PLA, by polymerization of *rac*-lactide, which can show enhanced properties compared to isotactic PLA and is more easily prepared than stereocomplex PLA [21].

Stereoblock PLA has short isotactic blocks (sequences) within the same polymer; it can also undergo co-crystallization, although not to the same extent as stereocomplex PLA. Consequently, lower melting points are obtained for stereoblock PLA compared to stereocomplex PLA; however, they exceed those of isotactic PLA. The melting points of stereocomplex PLA are dependent on the block length.

There are two forms of PLA with alternating stereochemistry along the polymer backbone: heterotactic PLA (disyndiotactic), obtained from *rac*-lactide, and syndiotactic PLA, obtained from *meso*-lactide (Fig. 5c, d, respectively).

Metal complexes which initiate *rac*-LA ROP with a high degree of stereocontrol are currently an area of major research interest and have the potential to produce a spectrum of different materials [19, 21]. Much attention focuses on iso-selectivity as this can enable production of PLA of good thermal resistance (isotactic, stereoblock or even stereocomplex PLA). There are two mechanisms by which an initiator can exert iso-selectivity in *rac*-LA ROP: (1) an enantiomorphic site control mechanism or (2) a chain end control mechanism. Enantiomorphic site control occurs using chiral initiators (Fig. 6); it is the chirality of the metal complex which

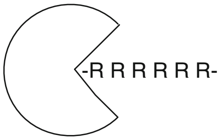


Fig. 6 Enantiomeric site control

i i i i i s i i i i i
- R R R R R R S S S S S S - polymer 1 CEC

i i i s i s i i i i i
- R R R R S S R R R R R R - polymer 2 ESC

Fig. 7 Polymer 1, chain end control; polymer 2, enantiomeric site control, where i and s are the relative stereochemistry of a pairwise addition of lactide units, *i* isotactic enchainment, *s* syndiotactic enchainment

controls the selectivity for a particular enantiomer of lactide. The isotacticity of the PLA chain is imparted by the metal centre by its selectivity.

In the chain end control, the stereochemistry of the last inserted lactide unit influences the selectivity for a particular stereochemistry of lactide. Chain end control mechanisms can be invoked for the preparation of iso- or heterotactic PLA. For iso-selective polymerization of *rac*-LA, the two mechanisms can be differentiated on the basis of the stereoerrors or defects; this is illustrated in Fig. 7.

When the stereocontrol occurs by a chain end control mechanism, a stereochemical defect results in the stereochemistry of the defect being propagated along the chain until the next defect occurs (polymer 1 in Fig. 7). If a stereochemical defect occurs in a polymerization using an initiator that exhibits enantiomeric site control, the mistake will be rectified with the next incoming lactide unit (polymer 2 in Fig. 7). This is because it is the chirality of the metal centre which determines the PLA tacticity and not that of the last inserted lactide unit.

The PLA tacticity (and stereocontrol mechanism) can be assessed by analysis of the NMR spectrum of the PLA. This can be carried out either by analysis of the homonuclear NMR spectrum, at the tetrad level, or by analysis of the $^{13}C\{^{1}H\}$ NMR spectrum (carbonyl region). An illustration showing the assignment of the tetrads in the methane region of the homonuclear decoupled $^{1}H\ \{^{1}H\}$ NMR spectrum is included in Fig. 8.

The ratios of the minor defect tetrads resulting from stereoerror (i.e. not iii, in the case of isotactic PLA) can be used to determine which mechanism is operating. For a chain end control and enantiomeric site control, the relative integrals should be in the ratio 1:1:1 (sii/isi/iis) or 1:2:1:1 (iis/isi/sis/sii), respectively [21].

The P_{i} (sometimes denoted P_{m}) is for the probability of forming a new *i*-dyad; the value is also obtained by comparison of the experimentally determined tetrad integrals with the probability that a particular tetrad would occur. P_{s} (sometimes denoted P_{r}) is the probability of forming a new *s*-dyad. The probabilities of a particular tetrad stereochemistry can be calculated using Bernoullian statistics (see Table 2). For a value of $0 < P_{\mathrm{i}} < 0.5$, the polymerization proceeds preferentially through a

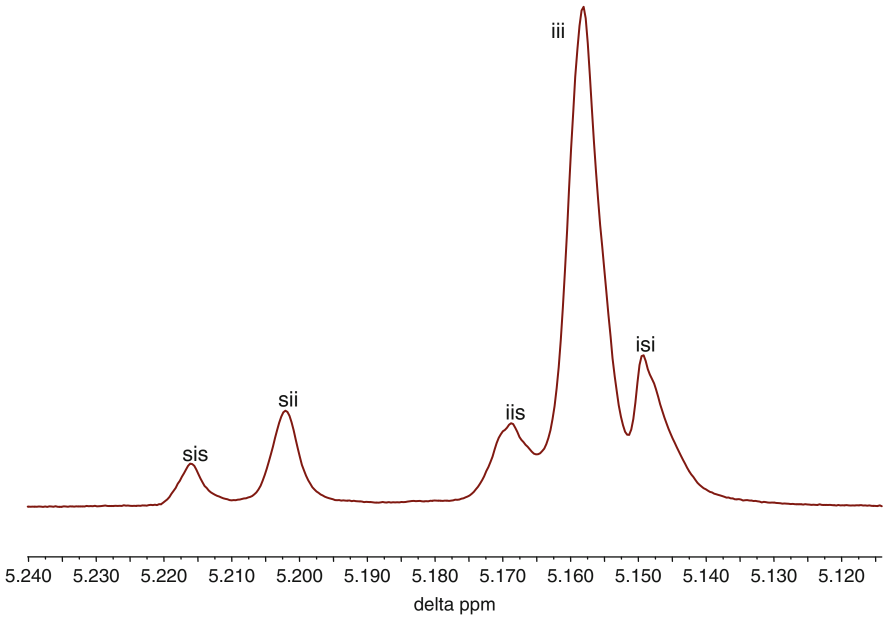


Fig. 8 Methine region (homonuclear decoupled ^{1}H {^{1}H} NMR spectrum) of moderately isotactic PLA ($P_i = 0.69$)

Table 2 *rac*-Lactide tetrad probabilities based on Bernoullian statistics

Tetrad	Probability
sis	$\frac{P_s^2}{2}$
sii	$\frac{P_sP_i}{2}$
iis	$\frac{P_sP_i}{2}$
iii	$P_s^2 + \frac{P_sP_i}{2}$
isi	$\frac{P_s^2+P_sP_i}{2}$

syndiotactic pair addition, and for a value of $0.5 < P_i < 1$, the polymerization proceeds preferentially through an isotactic pair addition. The probability of a highly isotactic polymer increases the closer the P_i value is to 1 [25].

Although a wide range of metal complexes have been found to be active in the polymerization of lactide, this review focuses on groups 3 and 13 initiators as they show particularly interesting properties. In particular, the initiators of group 3 show excellent rates of polymerization and, in some cases, good polymerization and stereocontrol. The group 13 initiators are generally rather sluggish; however, they show some of the highest degrees of polymerization and stereocontrol. The review will highlight selected examples of initiators in these two groups of the periodic table; in particular, initiators displaying high rates or high degrees of control will be highlighted.

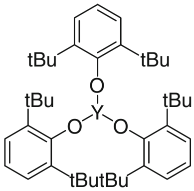


Fig. 9 [*SS*-LA]/[ROH]/[YL_3] 50:1:0.3 M, CH_2Cl_2, 25°C, 100%, 2 min

2.2 Group 3 Catalysts

Group 3 complexes, particularly those of yttrium, have attracted a large amount of interest as initiators for LA ROP, predominantly due to the high rates and lack of toxicity of the complexes and by-products [19].

2.2.1 Homoleptic Alkoxide Complexes

The first reports of LA ROP using yttrium complexes focused on homoleptic alkoxide complexes, such as cluster complexes of the form $Ln_5(\mu\text{-O})(OR)_{13}$ [27]. A patent, and preprint, published by DuPont described the application of a homoleptic yttrium alkoxide, $Y(OCH_2CH_2NMe_2)_3$, formed in situ by reaction of yttrium *tris*-*iso*-propoxide with *N*,*N*-dimethylaminoethanol. The complex showed a very high rate ($k_{obs} = 0.5\ s^{-1}$, $[Y]_0 = 3$ mM) and reasonable polymerization control [28].

Stevels et al. studied homoleptic yttrium aryloxide complexes (Fig. 9) [29]. The complexes were rather slow initiators; however, in the presence of isopropanol, the rate was accelerated and the polymerization control was excellent.

2.2.2 Heteroleptic Complexes

A wide range of heteroleptic yttrium alkoxide, or more commonly amide, complexes have been reported as initiators. In order to enable controlled, single-site polymerization to occur, it is usual to apply a dianionic (or two monoanionic) ligand; a range of different donors have been investigated. Salen, guanadinate, *bis*(naphtholate), 1,4,7-thiazacyclononane and 1,ω-dithiaalkanediyl-bridged *bis*(phenolate) ligands all showed good to fast activity [21, 30–34]. Ambidentate, *bis*(thiophosphinic amide), *bis*(phenoxy)amine and *bis*(oxazolinate) ligated complexes all showed rapid initiation in the ROP of LA [35–39]. A key challenge for group 3 initiators is the preparation of complexes which show acceptable rates and polymerization control, particularly stereocontrol. This section will highlight some of the promising yttrium complexes for stereocontrolled *rac*-LA ROP.

Okuda et al. have investigated a series of yttrium, scandium and lutetium complexes with 1,ω-dithiaalkanediyl-bridged bisphenolato (OSSO) ligands; a

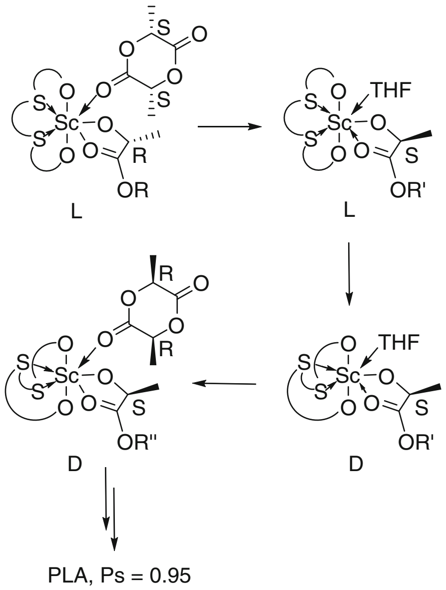


Fig. 10 Proposed mechanism of stereocontrol

range of different phenolate substituents and bridging groups on the ancillary ligand have been investigated (**4**) [31, 40]. Some of the complexes show a high degree of heteroselectivity, with scandium complexes producing PLA with a P_s as high as 0.94 and the yttrium complexes showing P_s up to 0.88. This increased heteroselectivity for the scandium complexes is attributed to its small ionic radius, enabling the ancillary ligand to exert a more significant steric shielding/directing effect. Okuda and co-workers have discovered that the P_s can be increased by changing length of the bridging unit and the bulk of the *ortho*-substituent on the phenolates. In an important development, Okuda proposed that the stereochemistry is controlled by a dynamic complex-monomer exchange process, as illustrated in Fig. 10.

The two enantiomers of the racemic initiator, Λ and Δ, each show a particular selectivity for a certain enantiomer of lactide. As the enantiomers of the group 3 complexes are undergoing dynamic exchange, it is proposed that heteroselectivity arises due to the complex isomerization occurring more rapidly than lactide insertion. Thus, the Λ complex isomer is selective for *SS*-lactide enchainment; after ring opening, it undergoes rapid conversion to the Δ isomer, which is selective for the *RR*-lactide enantiomer. This rapid exchange between the Λ and Δ isomers of the initiator combined with the high selectivities each shows for a particular enantiomer leads to the formation of highly heterotactic PLA. This type of mechanism has subsequently been invoked by other research groups, in particular for initiators based on group 4 elements, to rationalize stereocontrol [41].

Carpentier and his research team have been prominent in the development of new group 3 initiators [33, 34, 42]. They were the first to report the use of the amine *bis* (phenolate) ligand system, which has now been widely investigated. An example is

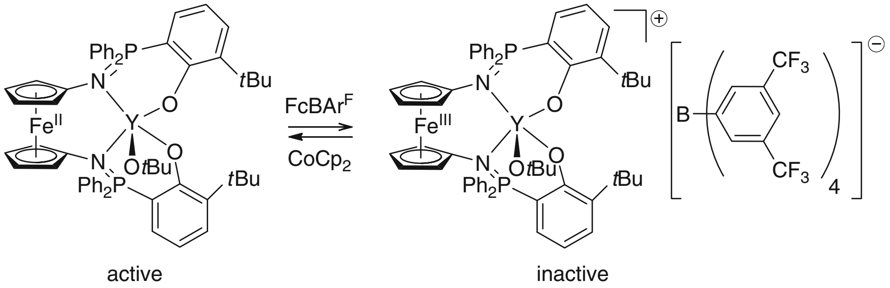


Fig. 11 Oxidation/reduction of ferrocene-containing complex

complex **3,** coordinated by an (ONO(O))-type ligand, which produces highly heterotactic PLA ($P_i = 0.95$) [43]. Carpentier's group and others have extensively investigated this class of ligands; of particular importance is the nature of the phenolate substituent, with more sterically hindered substituents at the 2-position enhanced heteroselectivity is observed [Cl ($P_r = 0.56$) < CMe_3 ($P_r = 0.80$) < CMe_2Ph ($P_r = 0.90$) < CMe_2 ($4CF_3$-Ph) ($P_r = 0.93–0.94$) ≤ $CMe_2{}^t$Bu ($P_r = 0.94–0.95$) ≤ CPh_3 ($P_r = 0.95–0.96$)] [43]. The electronic nature of the substituents appears to exert much less of an influence. The related ONO(N)-type ligand system has been investigated, by Mountford and colleagues, using a range of metal centres, including samarium, lanthanum and indium [44–48]. In 2010, they reported a zwitterionic yttrium initiator (**2**) which enabled initiation from exogenous primary and secondary amines [45]. Polymerizations are conducted in the presence of benzylamine, producing PLA with a benzylamide end group with excellent control. MALDI-ToF mass spectrometry showed negligible transesterification, and the initiator showed a strong heterotactic bias (P_s up to 0.93)

Arnold and colleagues have reported a series of chiral homoleptic yttrium and lanthanide *tris*(alkoxide) complexes [49, 50]. These initiators (including complex **1**) show high degrees of iso-selectivity and rapid rates, even at low temperatures. Thus, using the racemic mixture of the lanthanide initiator, stereoblock PLA was produced with a P_i of 0.81; so far, this is the only known type of yttrium initiator able to exert such stereocontrol and a very exciting finding. Analysis of the stereoerrors indicates that an enantiomorphic site control mechanism is responsible for the iso-selectivity.

Redox active ancillary ligands were first used to control lactide polymerizations using titanium complexes [51]. Very recently, Diaconescu and co-workers have reported derivatives of salen complexes incorporating a ferrocene unit which can be oxidized and reduced to switch the polymerization "OFF" and "ON", respectively (Fig. 11) [52, 53].

The reduced yttrium complex was active for the polymerization of *SS*-lactide, 74% conversion in 3 h (0.2 M, THF, 25°C). When the complex was oxidized, using $FcBAr^F$, the polymerization was completely stopped, and it was restarted when the complex was reduced back. The authors provide good evidence that the polymerization "switch" operates by changing the electron density of the yttrium–alkoxide bond during oxidation/reduction cycles. Polymerizations with the indium analogue

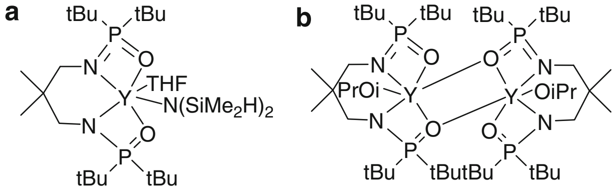


Fig. 12 (**a**) Mononuclear yttrium initiator; (**b**) dinuclear yttrium initiator

were considerably slower and showed an inverted behaviour when applied to the polymerization of trimethylene carbonate, i.e. the oxidized form of the complex was more active than the reduced form.

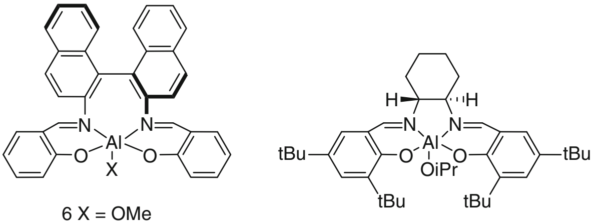
Our research groups have investigated various *bis*(thio/oxo phosphinic)diamido yttrium initiators (e.g. complex **5**) [36, 54–56]. These complexes show excellent rates for LA ROP and reasonable control; polymerization control is improved in the presence of exogenous alcohol. We have shown that the nuclearity of the initiator has an important influence over polymerization stereochemistry, with a mononuclear complex enabling high degrees of heteroselectivity (Fig. 12).

The stereochemical control is achieved via a chain end control mechanism, enforced by the steric bulk of the ligand. The dinuclear complexes cannot control the stereochemistry, leading to atactic PLA, due to the lack of a single, hindered lactide coordination site.

2.3 Group 13 Catalysts

Aluminium complexes for the polymerization of lactide have been described extensively in the literature, and much attention, particularly in the 1980s and 1990s, focused on homoleptic aluminium alkoxide (*iso*-propoxide) complexes or aryloxide complexes; in some cases, the alkoxide group was generated in situ [23, 57, 58]. Aluminium is also very well known as the metal centre with greatest precedent for yielding iso-selective catalyst. The first example of a highly iso-selective catalyst was from the Spassky research group in 1996 [59]. They reported the salen–aluminium complex, **6**, which was found to preferentially polymerize the *RR*-enantiomer of *rac*-lactide, with moderate to low activity and up to 50% conversion (Fig. 13).

Coates and co-workers reported polymerizations using both the enantiomerically pure (**7**) and the racemic (**8**) *iso*-propoxide analogues [21]. Complex **8** polymerized *rac*-lactide iso-selectively producing stereoblock PLA ($P_i = 0.96$). The iso-selectivity was achieved due to the high selectivity of **7** for *RR*-lactide and corresponding *S*-enantiomer for *SS*-lactide. Further studies of the aluminium–salen system have led to the proposal that several factors influence the polymerization



6 X = OMe
7 X = OiPr
8 X = OiPr

Fig. 13 Salen–aluminium alkoxide initiators

mechanism of these complexes: the chirality of the N–N backbone, the helicity of the η^4 chelate (Δ or Λ conformation), the chirality of the alkoxide as well as the choice of solvent [60]. Modifications of the salen ring, including half-salen complexes, have led to similarly high levels of stereochemical control [61–64].

2.3.1 Gallium and Indium Initiators

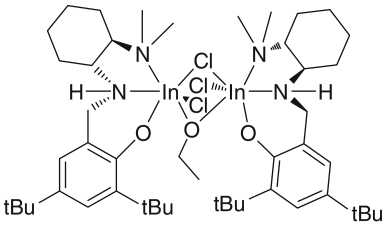
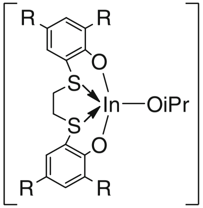
Other metals in group 13 have not been investigated nearly as extensively as aluminium. Recently, however, indium and gallium complexes have been shown to be active initiators; in particular, indium complexes are quite desirable due to their low toxicity and water tolerance [65–67]. Table 3 illustrates some selected examples of interesting Ga and In initiators.

The first indium complex reported for LA ROP was ligated by a diaminophenolate group (**9**), a ligand related to those that have previously shown very good activity in zinc-catalysed LA ROP [68, 73]. A fast rate was reported and resultant PLA showed a slight isotactic bias (max. $P_{\mathrm{i}} = 0.62$). The use of an ancillary ligand may not be essential for indium initiators, as demonstrated in an interesting recent report from the groups of Tolman and Hillmyer. They showed that an initiating system comprising indium(III) chloride, benzyl alcohol and triethylamine yielded highly heterotactic PLA with good rates and a high degree of polymerization control [69, 70]. Figure 14 illustrates the proposed mechanism for the ROP.

The initiating system yields PLA with P_{s} values as high as 0.97. The polymerization control is also good, with PLA of $M_{\mathrm{n}} = 159{,}000$ g/mol and narrow PDI values (between 1.06 and 1.12) and only a small degree of transesterification being observed. MALDI-ToF spectrometry showed that the PLA chains were end-capped with benzyl ester groups. The polymerization was first order in [$InCl_3$] and [LA], and zero order with respect to [BnOH] and [NEt_3]. The rate was observed to slow when other indium(III) halides were used in place of $InCl_3$, suggesting the halide group is present in the active species. An X-ray crystal structure of the active species could not be isolated; however, an aqua complex was determined, and from this, it was deduced that the initiator was likely an $[InCl_{(3-n)}(OR)_n]_m$ species.

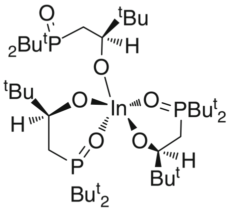
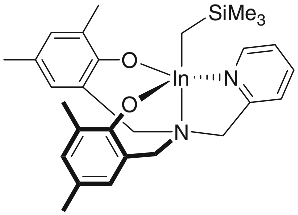
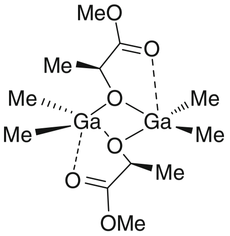
Okuda and co-workers have applied the tetradentate (OSSO)-type ligands to prepare both aluminium and indium complexes, both of which are active for LA

Table 3 Group 13 initiators

Initiator/initiating system	Solvent (T/°C) $[\mathrm{I}]_0$:$[\mathrm{LA}]_0$	Activity	P_i/P_s	Reference
 **9**	DCM (25) 1:200	30 min, 90%, $k_{obs} = 0.59\ \mathrm{s}^{-1}\ \mathrm{m}^{-1}$	$P_i = 0.59$	[68]
InCl$_3$, BnOH, NEt$_3$ **10**	DCM (25) 1:1(BnOH):2(NEt$_3$):100	5 h, 98%, $k_{obs} = 2.3 \times 10^{-4}\ \mathrm{s}^{-1}$ ($[\mathrm{LA}]_0 = 0.84$ M)	$P_s = 0.94$	[69, 70]
 R = CMe$_2$Ph **11**	Toluene (100) 1:100 (*SS*-LA)	4 h, 99%		[65]

(continued)

Table 3 (continued)

Initiator/initiating system	Solvent (T/°C) $[I]_0$:$[LA]_0$	Activity	P_i/P_s	Reference
 **12**	DCM (25) 1:624	2.5 h, 56%	$P_i = 0.63$	[71]
 **13**	Toluene (70) 1:100	6 h, 94%, $k_{obs} = 0.76\ h^{-1}$ ($[LA]_0 = 1.0$ M)	Atactic	[44]
 **14**	THF (25) 1:250	144 h, 97%	$P_s = 0.68$	[72]

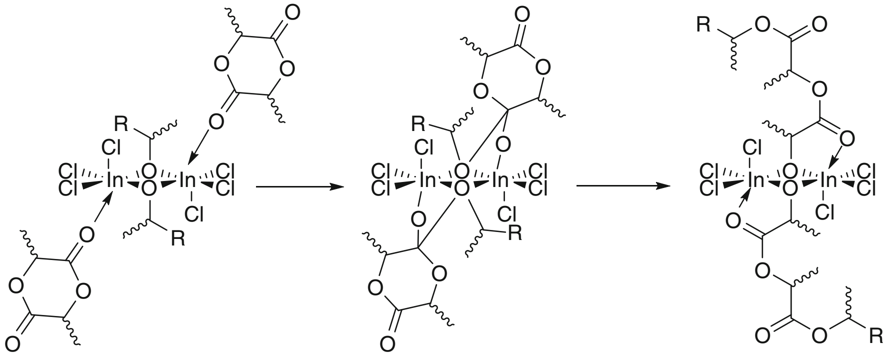


Fig. 14 Postulated structure and polymerization scheme

ROP [65, 74]. The indium alkoxide (**11**) was a good initiator, with 100 equivalents of *SS*-lactide being converted to PLA in 200 min, at 50°C. When compared with the analogous aluminium initiators, the indium complexes showed comparable rates but lower-molecular-weight PLA. All the PLA formed from *rac*-lactide was atactic [65].

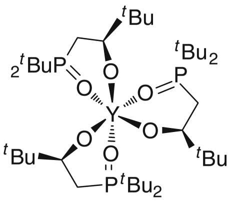
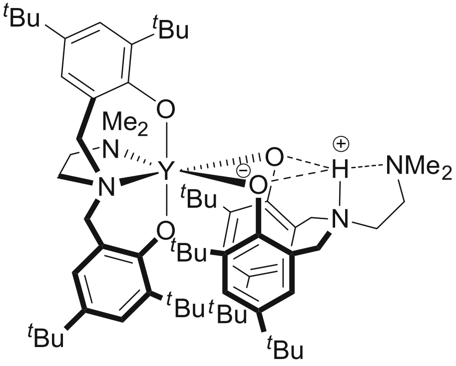
Okuda and Arnold have reported a series of 5- and 6-coordinate chiral indium complexes (e.g. **12**), analogous to those previously discussed with yttrium (Table 4), which show varying activities for the polymerization of *rac*-lactide [71]. The homoleptic species was fluxional, interconverting between a 5-coordinate and *fac*- and *mer*-isomers of a 6-coordinate complex. It resulted in controlled polymerization and some stereoselectivity (max. $P_i = 0.63$ and max. $P_s = 0.64$). MALDI-ToF mass spectrometry confirmed that the chiral alkoxide ligand was an initiating group.

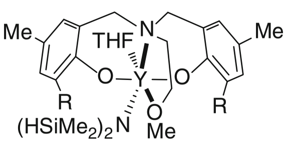
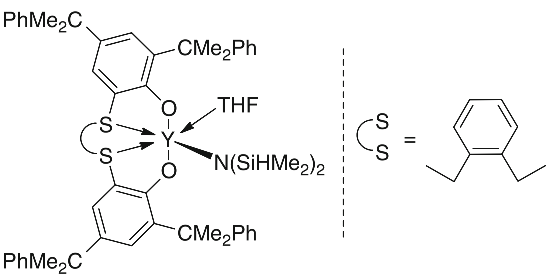
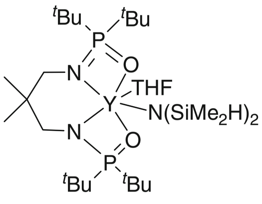
Mountford's group has published work on *bis*(phenolate)amine indium initiators ((ONO(N))-type ligands) [44]. The polymerizations reached high conversions, but activity ranged from good to moderate, with complex **13** (the fastest initiator) enabling complete conversion after 6 h (1:100 [I]:[LA], 1 M [LA], toluene, 70°C). The experimental M_n values were higher than calculated M_n values, indicating that just 15–50% of the indium complex initiates. This lack of correlation can be attributed to the poor initiating capability of the CH_2SiMe_3 group, with polymerization control that is much improved when carried out with exogenous $BnNH_2$, producing amine-terminated PLA.

In 2001, Chisholm's group reported a β-diiminate (BDI) gallium–$OSiMe_3$ complex which was unreactive for LA ROP; the authors cited substrate binding as the limiting step [76]. Recently, a gallium alkoxide initiator (**11**) has been reported as an efficient polymerization initiator [72]. The dimeric complex was formed by reaction of $GaMe_3$ with (*S*)-methyl lactate (Fig. 15).

Polymerizations using *rac*-lactide yielded PLA with (*S*)-methyl lactate end groups. The molecular weights corresponded to initiation from both alkoxide

Table 4 Group 3 initiators

Initiator/initiating system	Solvent (T/°C) $[\mathrm{I}]_0$:$[\mathrm{LA}]_0$	Activity	P_i/P_s	Reference
 **1**	DCM (−18) 1:200	10 min, 98%	$P_i = 0.81$	[50]
 **2**	THF (25) 1:5($BnNH_2$):100	20 min, 89%	$P_s = 0.93$	[75]

 R = CMe$_2$(CF$_3$Ph) **3**	THF (20) 1:200	1 h, 79%	$P_s = 0.95$	[43]
 **4**	THF (25) 1:300	30 min, 85%	$P_s = 0.86$	[40]
 **5**	THF (25)	100% $<$ 10 min $k_{obs} = 8.36 \times 10^{-3}\ s^{-1}$	$P_s = 0.85$	[54]

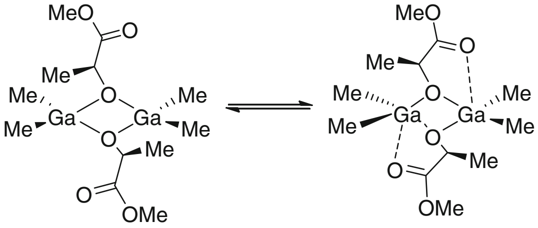


Fig. 15 Proposed structure of initiator

groups in the dimer. Atactic PLA was produced at 40°C in DCM, but when γ-picoline was added to the polymerization mix, a modest heterotactic bias was observed. Horeglad et al. rationalize the activity due to the strong Ga–Me bond weakening the Ga–OR bond, thereby favouring lactide insertion [72].

3 Carbon Dioxide/Epoxide Copolymerization

3.1 Introduction

Carbon dioxide is a particularly attractive alternative chemical feedstock [77]; it is highly abundant, non-toxic, available as the waste product of many industrial processes and, hence, relatively cheap. In addition, carbon dioxide is the most abundant of the greenhouse gases (ghg); the increasing concentration of ghg is predicted to cause a rise in global temperature, with associated dangers. There is, thus, extensive focus on carbon capture and storage in order to mitigate CO_2 emissions; an attractive economic driving force is to develop methods to use captured carbon dioxide to make useful products [78–80]. Whilst nature successfully transforms CO_2 into carbohydrates, via photosynthesis, synthetic chemistry has been less successful. Indeed, the CO_2 molecule is highly stable, being the most oxidized form of the carbon atom, and there is a clear role for catalysis in reducing activation energies. To date, there are only a limited number of such reactions, including the synthesis of urea, inorganic carbonates, methanol, salicylic acid, organic carbonates and copolymers [81–85]. Various copolymers can be synthesized by the sequential copolymerization of CO_2 and strained heterocyclic molecules, including epoxides, aziridines, episulfides and oxetanes [86–88], the most widely studied being the copolymerization with epoxides [mostly propylene oxide (PO)] to produce polycarbonates (Fig. 16) [89–98].

Polycarbonates are already commercially produced and have excellent properties including electrical insulation, transparency and heat resistance; they have been applied in the manufacture of a range of products, from adhesives to compact disks, encapsulation of electrical and electronic parts, optical lenses and in packaging. Most of these polycarbonates have a poly(oxycarbonyloxy-1,4-phenylene

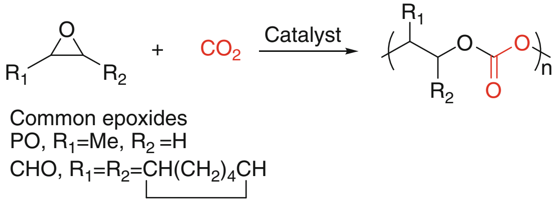


Fig. 16 The sequential copolymerization of epoxides and CO_2

isopropylidene-1,4-phenylene) structure (known by the generic name "polycarbonate"). This polymer is made from the highly toxic phosgene (carbonyl chloride) and bisphenol A (BPA), a suspected carcinogen [99]. Very recently, several countries, in addition to the EU, have banned production of drinking bottles (particularly for infants) produced from BPA, due to toxicity concerns [100].

Currently, only a limited range of aliphatic polycarbonates, produced from CO_2, are being manufactured, including poly(ethylene carbonate) (PEC), poly(propylene carbonate) (PPC), poly(butylene carbonate) (PBC) and poly(cyclohexene carbonate) (PCHC) [101]. The properties of these materials differ from polycarbonate, but they do offer an attractive sustainable alternative, in particular for commodity applications, including packaging, engineering polymers and elastomers. Also important is that the production costs and properties of these materials still need to be improved to allow widespread impact. The selection of the copolymerization catalyst is of critical importance as it impacts both the efficiency of the process (cost) and the properties of the resulting polycarbonates. Catalysts for CO_2/epoxide copolymerization reactions have been comprehensively reviewed [89–98]; therefore, this chapter will only present the most recent trends, including bimetallic complexes, binary linked and dinuclear salen systems.

3.2 Reaction Mechanism and Side Products

The copolymerization of CO_2 and epoxides is proposed to occur via a coordination–insertion mechanism (Fig. 17). It is catalysed by various Lewis acidic metal halides, carboxylate or alk/aryloxide complexes (LMX complexes where L is the ancillary ligand, M is the metal centre and X is the co-ligand). The metal complex initiates the copolymerization by coordinating the epoxide and attacking it with the nucleophilic co-ligand X (halide/carboxylate, if the X group is an alkoxide/aryloxide, the initiation step is CO_2 insertion [102]), leading to epoxide ring opening and formation of a metal alkoxide. The metal alkoxide inserts CO_2 to form a metal carbonate. The cycle propagates by nucleophilic attack of the metal carbonate on a coordinated epoxide, producing a new metal alkoxide, which inserts CO_2 once again, and so on. Multiple repetitions of this series of reactions lead to copolymerization and to a copolymer with only carbonate linkages.

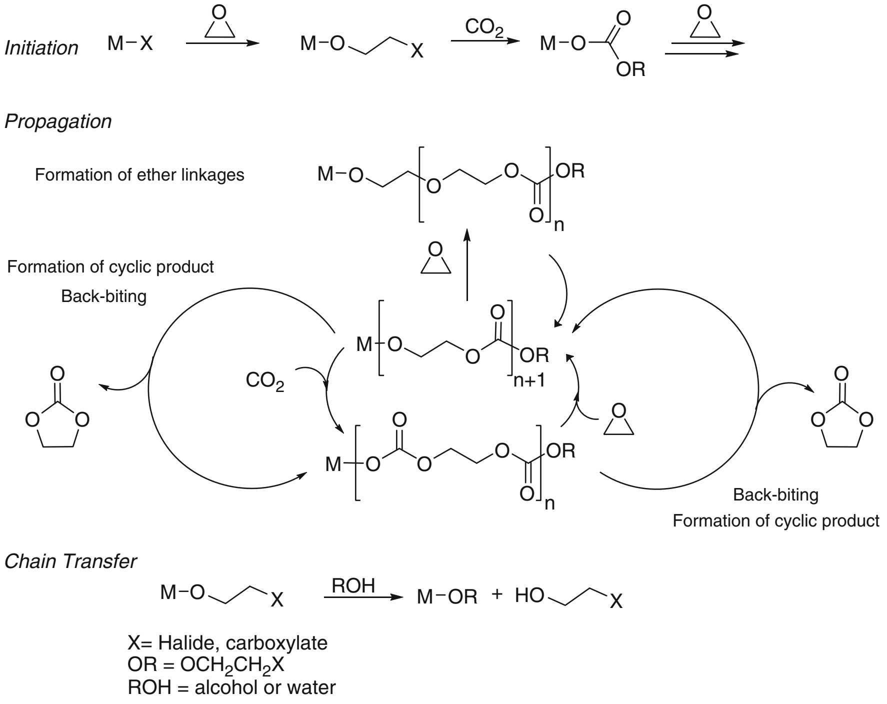


Fig. 17 Proposed catalytic mechanism for the copolymerization of CO_2 and epoxides

In order that an alternating copolymer is produced, the metal alkoxide must undergo faster insertion of carbon dioxide than reaction with a second equivalent of epoxide. If the metal alkoxide reacts with a second epoxide or undergoes decarboxylation reactions, ether linkage(s) may be formed. Ether linkages are undesirable as they compromise the properties of the polymer and reduce the carbon dioxide uptake.

In a controlled copolymerization, the initiation reaction occurs more rapidly than propagation and leads to a degree of polymerization (DP), and correlated average molecular weight (M_n), dependent on the concentration of catalyst. During the copolymerization, chain transfer can occur either intramolecularly leading to backbiting or by reaction with externally added chain transfer agents, including alcohols/water/protic acids:

1. The backbiting reaction occurs when the metal alkoxide (or carboxylate) chain end attacks a carbonate (or ether) linkage in the main chain forming a cyclic carbonate by-product and regenerating a metal alkoxide (or carboxylate)/X species [103]. Five-membered ring carbonates are thermodynamically stable and do not undergo any further ring-opening polymerization; they are often produced as by-products.
2. Chain transfer reactions can occur if the reaction mixture is exposed to alcohols or water (this frequently occurs via contaminants), forming a hydroxyl-

terminated copolymer chain and a new metal alkoxide/hydroxide species, which can initiate/propagate [104, 105]. Immortal polymerization occurs when the rate of chain transfer exceeds chain propagation; it leads to a reduction in the DP (M_n) but still enables chains of narrow dispersity to be produced [106]. Immortal polymerization can find interesting applications such as sequential controlled multi-block copolymerization [107, 108].

3.3 From the Early Developments to Low-Pressure Homogeneous Catalysts

The copolymerization of carbon dioxide and epoxides has been known since the late 1960s. In 1969, Inoue et al. reported that propylene oxide (PO) could copolymerize with CO_2, at 80°C and elevated pressures (50–60 bar), using catalyst made in situ by mixing $ZnEt_2$ and stoichiometric quantities of water [18]. The catalyst was slow ($TOF = 0.12\ h^{-1}$) but inspired further research. During the following decade, a range of heterogeneous catalysts, produced by reacting between dialkylzinc reagents or zinc oxide and diols, for example, pyrogallol or 4-bromopyrogallol, were developed leading to increased activities ($TOF = 1\ h^{-1}$) [95]. Subsequently, the most effective heterogeneous catalyst was zinc glutarate, produced by reaction between $Zn(OH)_2$/ZnO and glutaric acid. Zinc glutarate has been extensively investigated and even commercialized, despite the high catalytic loading needed [91]. Double metal cyanides (DMCs), i.e. $Zn_3[M(CN)_6]_2$, where M = Fe(III) or Co(III), also proved to be a promising class of heterogeneous catalysts despite issues with CO_2 incorporation [89]. Overall, heterogeneous catalysts have been somewhat hampered by the difficulty in defining the active catalyst sites and in understanding structure/activity relationships. This, combined with problems ensuring high carbon dioxide uptake and highly polydisperse polymers, has driven the development of well-defined, homogeneous catalysts.

3.3.1 Homogeneous Catalysts

In 1978, Inoue reported the first example of a single-site catalyst, a tetraphenylporphyrin aluminium chloride complex (Fig. 18a), which was used with $EtPh_3PBr$ as a co-catalyst [109, 110]. The complex was used to copolymerize PO and carbon dioxide: it was very slow (taking up to 23 days) but did produce PPC of low molecular weight and narrow PDI. Later, in 2003, the manganese(III) acetate analogue of this complex was the first example of a catalyst capable of copolymerizing CHO and CO_2 under 1 atm pressure.

The development of discrete zinc bisphenoxide complexes (Fig. 18b) was an important advance, mostly led by Darensbourg [111–113] and Kuran [114–116]. These catalysts produced high-molecular-weight polymer (M_n of 42,000 g/mol);

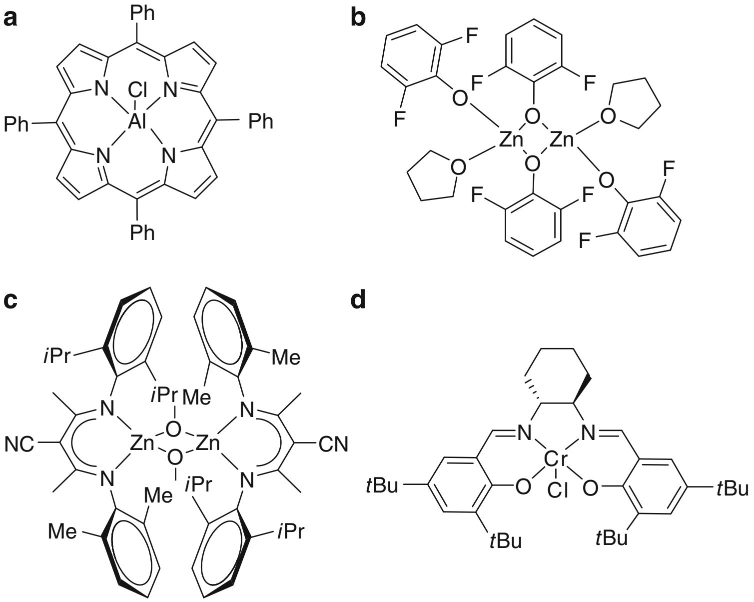


Fig. 18 Representative examples of homogeneous catalysts for CO_2/epoxide copolymerization: Inoue's tetraphenylporphyrin aluminium chloride complex (**a**), zinc *bis*-2,6-fluorophenoxide complex (**b**), zinc β-diiminate complex (**c**) and chromium–salen complex (**d**)

however, they often showed quite large polydispersity indices (up to 6, probably due to catalyst aggregation). In addition, catalysts were also active for epoxide homopolymerization, which resulted in a high percentage of ether linkages in the copolymers.

In 1998, Coates and co-workers reported a series of β-diiminate (BDI) zinc catalysts (BDI) active for copolymerization of cyclohexene oxide (CHO)/CO_2 (Fig. 18c). They showed that minor variations in the stereoelectronic nature of the BDI ligand led to dramatic changes in catalytic activity [117–120]. Moreover, the zinc BDI catalysts could be tailored to achieve high activities in PO/CO_2 copolymerization [121]. In a detailed mechanistic study, Coates reported that some of the complexes underwent dimerization reactions under the conditions of the catalysis and this was central to controlling reactivity [102]. The formation of dimers was dependent on the size of the substituents attacked to the phenyl rings on the BDI ligand. They found that strongly bound dimers and monomers (formed from bulky BDI substituents) showed only low activity, whilst loosely bound dimers were very active catalysts (producing PCHC with molecular weights of up to 27,000 g/mol).

Coates proposed that the mechanism involved a "bimetallic" pathway (Fig. 19), with one metal coordinating the epoxide, whilst the second metal bound the carbonate group (growing polymer chain) which attacked and ring-opened the epoxide. This mechanistic proposal has since led to the preparation of many dizinc (and other dinuclear) complexes (see Sect. 3.4).

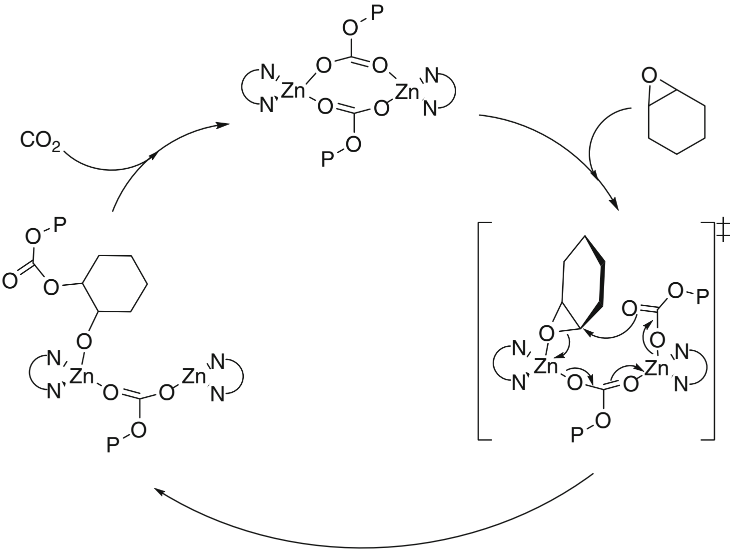


Fig. 19 Bimetallic catalytic mechanism and proposed bimetallic transition state

Perhaps the most widely investigated ligand type so far has been the *N*,*N*′-ethylenebis(salicylimine) or salen (Fig. 18d) [91]. The field of metal salen catalysts was comprehensively reviewed in 2007 by Darensbourg [91]; therefore, only a brief overview of important developments up until this point has been included. In 2000, Jacobsen and co-workers reported, in a patent, that chiral chromium salen complexes were viable catalysts for the production of polycarbonates [122]. Later, and independently, Darensbourg and co-workers reported that a salen chromium chloride complex was as an excellent catalyst for the copolymerization of CHO and CO_2 [123]. The catalyst required the addition a nucleophilic co-catalyst (*N*-MeIm) which was found to bind to the metal centre *trans* to the chloride (the initiating group). This *trans* ligation led to a weakening of the metal–initiator bond (Cr–Cl) and facilitated both initiation and propagation reactions. Subsequently, there have been many reports to modified metal salen catalysts enabling improvements to the activity, selectivity and molecular weight [124–131]. Moreover, these systems have been optimized for the selective production of PPC from propylene oxide and CO_2 by employing a salen ligand with a rigid phenylene backbone [103, 132, 133]. Other variations have included changes to the initiating group (e.g. OAc or N_3), the co-catalyst (including neutral Lewis bases, such as DMAP, or ionic species, e.g. [PPN]Cl), the ligand (by partially or fully reducing the imine functionalities to obtain either salalen [134] or salan ligands)[135] and the metal centre (including complexes of Co[136] or Al [137]). In particular, the development of cobalt(III)–salen catalysts has been a breakthrough in terms of activity for CHO and PO at low pressures of CO_2 (Table 5).

Table 5 Comparison of selected catalysts for the copolymerization of CHO and CO_2

Catalyst	T (°C)	$p[CO_2]$ (bar)	TON[a]	TOF[b]	%Carbonate[c]	Selectivity[c]	M_n[d]	PDI[d]	Reference
A/$EtPh_3PBr$	20	48	100	0.3	>99	>99	6,200	1.06	[110]
B	80	55	2,000	45.8	>99	–[e]	42,000	6.00	[113]
C	50	7	380	2,290	90	>99	22,900	1.09	[121]
D/*N*-MeIm	80	58	3,040	127	>99	–[e]	8,900	1.20	[123]

[a] Mole CHO consumed per mole metal

[b] Mole CHO consumed per mole metal per hour

[c] Determined by ^1H NMR spectroscopy

[d] Determined by gel permeation chromatography (GPC) using polystyrene standards

[e] Not specified

3.4 Dinuclear Complexes

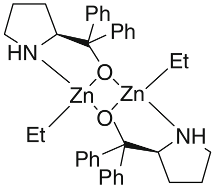
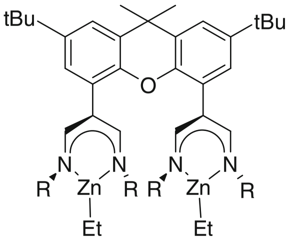
A common theme in this catalysis has been the proposal of dinuclear catalyst active sites, often termed "bimetallic" catalysis. This section will review various dinuclear and dimeric complexes which have shown activity for copolymerization.

In 1999, Nozaki and co-workers were the first to report an asymmetric copolymerization, catalysed by a chiral amino-alkoxide zinc complex **15** (Table 6) and producing optically active PCHC with 70% ee (measured by hydrolysing the copolymer and analysing the resulting diol using chiral GC) [138, 148]. The crystal structure of the catalyst, reported subsequently, showed a dimeric structure; it was unclear whether the dimer was maintained during the copolymerization [148]. In the solid state, the zinc–zinc distance in the catalyst was determined to be 3.00 Å (vs. ca. 4 Å, for the "loosely bound" BDI zinc dimers).

Following the detailed mechanistic study using BDI zinc complexes, Coates subsequently reported a dinucleating BDI ligand: the β-oxo-δ-diimine (BODDI) ligands (Fig. 20) [149]. The reaction of the corresponding dinuclear zinc ethyl complexes with acetic acid afforded zinc acetate systems (with a Zn–Zn distance of 3 Å), but no catalytic activity was reported.

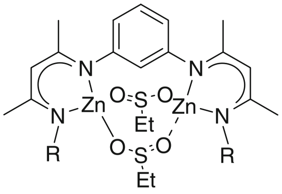
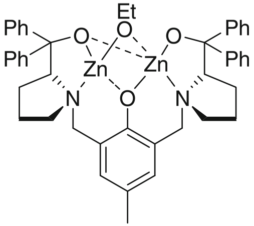
Other groups also developed novel bimetallic BDI ligand structures which place two zinc sites parallel to each other, rather than face to face. Based on xanthdim ligands, Hultzsch and co-workers synthesized, in 2007, two dizinc complexes (see example in Table 6, **16**), which showed low activity with CHO (max. TOF of 9 h^{-1}), probably due to the catalyst steric bulk [139]. Zn–Zn distances of 4.92 Å and 5.60 Å were reported for the fluorinated and non-fluorinated complexes, respectively. In 2008, Harder and co-workers used bridged β-diiminato ligands for the preparation of dinuclear zinc and calcium complexes. The calcium complexes were completely inactive, but the zinc analogues were active (with CHO). The zinc complexes were all characterized by X-ray diffraction experiments, with the Zn–Zn distances for the 1,4-phenylene,1,3- phenylene and 2,6-pyridylene complexes being 8.17, 6.10 and 3.79 Å, respectively. The most active catalyst was the *meta*-substituted complex (Table 6, **17**) which showed a TON of 1,196 and a maximum TOF of 262 h^{-1}, at 10 atm and 60°C. This catalyst yielded PCHC with

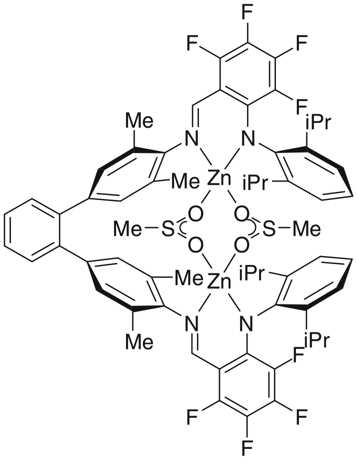
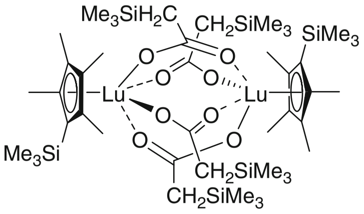
Table 6 Selected bimetallic recent catalysts for epoxide/CO_2 copolymerization

Epoxide	Catalyst	T (°C)	$p[CO_2]$ (bar)	TON[a]	TOF[b]	% Carbonate[c]	Selectivity[c]	M_n[d]	PDI[d]	Reference
CHO	 **15**	60	30	2,000	83	>99	>99	18,000	1.7	[138]
CHO	 R= 2,3-dimethylphenyl **16**	50	8	666	9.3	50	>99	16,700	2.7	[139]

(continued)

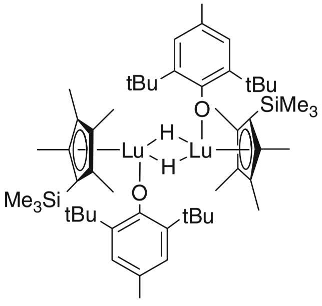
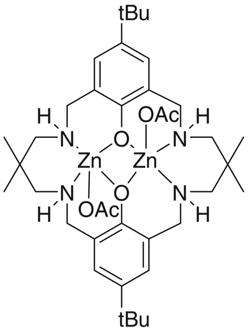
Table 6 (continued)

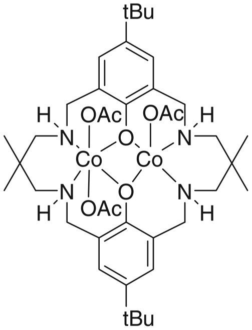
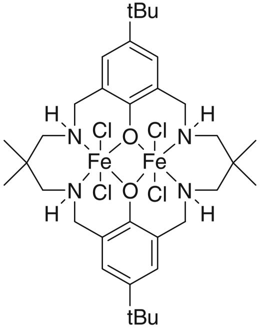
Epoxide	Catalyst	T (°C)	$p[CO_2]$ (bar)	TON[a]	TOF[b]	% Carbonate[c]	Selectivity[c]	M_n[d]	PDI[d]	Reference
CHO	 **17**	60	10	1,196	199	>99	>99	110,000	1.33	[140]
CHO	 **18**	80	20	285	142	71	>99	21,000	1.28	[141]

CHO	 **19**	80	14	9,930	2,860	79	>99	245,000	1.2	[142]
CHO	 **20**	90	12.2	240	5.0	94	>99	17,400	2.66	[143]

(continued)

Table 6 (continued)

Epoxide	Catalyst	T (°C)	$p[CO_2]$ (bar)	TON[a]	TOF[b]	% Carbonate[c]	Selectivity[c]	M_n[d]	PDI[d]	Reference
CHO	 **21**	110	12.2	226	9.4	>99	>99	24,700	6.15	[144]
CHO	 **22**	80	1	219	9	>99	96	6,200	1.19	[145]

CHO	 **23**	80	1	210	80	>99	>99	6,300 2,800	1.04 1.14	[146]
CHO	 **24**	80	10	1,285	54	>99	>99	17,200 8,100	1.03 1.06	[147]

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[a] Moles epoxide consumed per metal

[b] Moles epoxide consumed per metal per hour

[c] Determined by ^{1}H NMR spectroscopy

[d] Determined by GPC using polystyrene standards

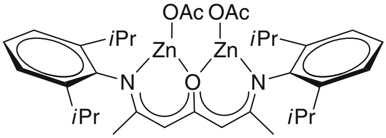


Fig. 20 Dinuclear BODDI zinc complex

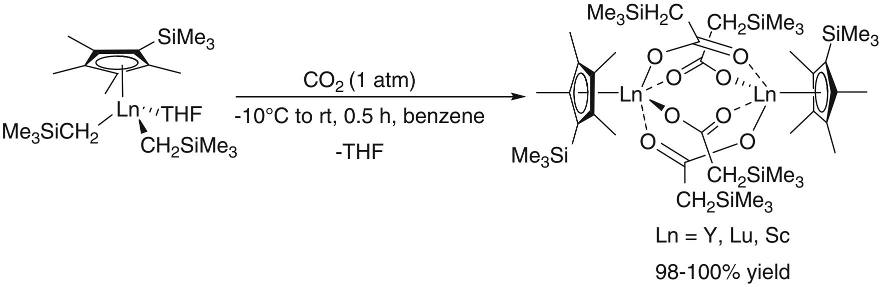


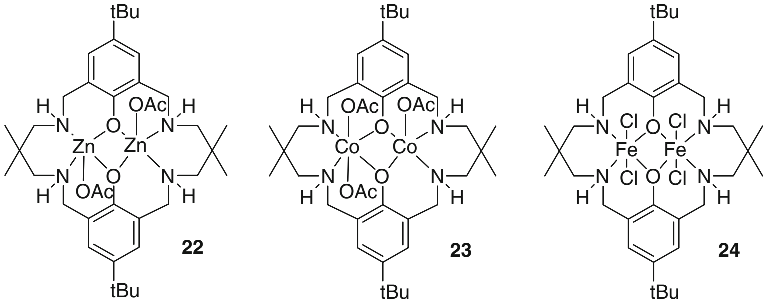
Fig. 21 Stoichiometric reaction of CO_2 with rare-earth metal alkyl complexes to produce carboxylate dimeric catalysts

99% carbonate linkages, high molecular weights (45,000–100,000 g/mol) and PDI between 1.20 and 1.40 [140].

In 2005, Xiao et al. reported a dizinc complex, coordinated by a pentadentate phenolate ligand, active for CHO/CO_2 copolymerization (see Table 6, **18**) [141]. The catalyst was prepared in situ by reaction between the protio-ligand, $ZnEt_2$ and ethanol. The structure proposed was **18**, and although a variety of alcohols were investigated, ethanol gave the best activity, producing PCHC with a TOF of 142 h^{-1} at 500:1 CHO/catalyst ratio, 20 atm and 80°C, and a selectivity for poly (cyclohexene carbonate) up to 99%. The catalyst was also active under just 1 atm CO_2 pressure, albeit a decreasing TOF of 3 h^{-1}. Replacing the two zinc centres with magnesium drastically reduced the activity [150].

In 2005, Lee and co-workers produced a series of dinuclear anilido-aldimine sulfinato zinc complexes [142]. Although the Zn–Zn distances changed only slightly from 4.88 to 4.69 Å for the "opened" and "closed" complex structures, respectively, the copolymerization activities were sensitive to the nature of the ligand scaffold. Thus, the opened catalyst was active, whereas the closed analogue was completely inactive. The difference in efficiency was attributed to better access of the monomers to the metal centres in the opened structure. Using the fluorinated versions of these complexes, the copolymerization with CHO reaction could be carried out efficiently at low catalyst loading (CHO/catalyst 50,000:1), with high TOFs (up to 2,860 h^{-1}) and producing PCHC of very high molecular weights (up to 284,000 g/mol) with polydispersities 1.3–1.7. This catalyst was active at 14 bar pressure of CO_2 (Table 6, **19**).

Multi-metallic heterogeneous catalysts of rare-earth metals (including Y and La) have proved effective [151]. Hou reported complexes of general formula



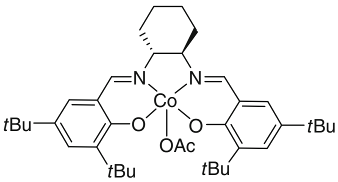
22 **23** **24**

Fig. 22 Main dinuclear Robson-type complexes developed by the Williams group

$[(C_5Me_4SiMe_3)Ln(CH_2SiMe_3)_2(THF)]$, (with Ln = Y, Dy, Lu, Sc), as well as related polyhydride complexes ($[(C_5Me_4SiMe_3)Ln(\mu\text{-}H)_2]_4(THF)_x$ with $x = 1, 2$) as single-component catalysts for the production of PCHC. Interestingly, the stoichiometric reaction of the *bis*(alkyl) complexes with CO_2 afforded the corresponding bimetallic tetra(carboxylate) complexes (Fig. 21), which also showed moderate activity for the alternating copolymerization (Table 6, **20**) [143].

The same group also showed that mono(cyclopentadienyl) mixed hydride/aryloxide dimer complexes of several lanthanide elements (Y, Dy, Lu) could be synthesized easily by the acid–base reaction between the mixed hydride/alkyl complexes and an aryl alcohol [144]. These complexes reacted with CO_2 to generate mixed formate/carboxylate derivatives, which were moderately active initiators for the copolymerization of CO_2 and cyclohexene oxide, without requiring a co-catalyst. The lutetium derivative **21** was the most active (at 110°C, TOF = 9.4 h^{-1}), yet despite a good selectivity (99% carbonate linkages), the molecular weight distribution remained broad (6.15) (Table 6).

In 2009, our group reported a dinuclear zinc acetate catalyst coordinated by a macrocyclic ligand for the copolymerization of CHO and CO_2 (Fig. 22 and Table 6, **22**) [145]. Copolymerization reactions could be carried out at pressures as low as 1 bar CO_2, with a TOF of 13 h^{-1} at 100°C (TOF = 70 h^{-1} at 10 bar CO_2) with very little cyclic carbonate (4%) produced and copolymers with a high proportion of carbonate linkages (>99%), low molecular weights (3,000–9,000 g/mol), but very narrow PDIs (<1.2). The trimetallic zinc analogue was easily formed in the presence of an excess of $Zn(OAc)_2$ but, despite reasonable activity at 1 atm pressure, was significantly less active than the bimetallic complex [152]. The macrocyclic ligand environment was also proposed to be key for the activity of the catalysts, as an "open" ligand analogue showed no activity [145]. Variation of the *para*-phenyl substituent showed that the electron-donating methoxy group significantly reduced the activity [152]. This was attributed to the lower Lewis acidity of the metal centre and a decreased binding and activation of the epoxide and CO_2. Based on analysis of the solid structures, obtained by X-ray diffraction, the Zn–Zn distances were approximately 3.1 Å for these complexes.



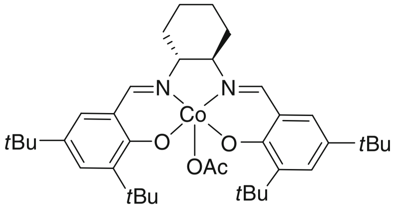
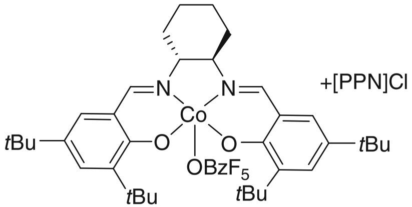
25

Fig. 23 Cobalt(III)–salen catalyst used by Coates and co-workers in 2003

The same ligand was used for the synthesis of dinuclear cobalt and iron catalysts for the copolymerization of CHO and CO_2. In the first case, the complexation was achieved by reaction between the ligand and cobalt(II) acetate which afforded the desired Co(II) compound, $[LCo_2(OAc)_2]$ [146]. Subsequent oxidation led to a mixed valence Co(II)/Co(III) compound (Fig. 22 and Table 6, **23**), with a Co–Co distance of 3.0 Å. Both complexes showed unprecedented activity for CHO copolymerization under 1 atm pressure of CO_2. At 100°C, **23** produced PCHC with a TOF of 250 h^{-1} (using 10 bar TOF raised to 1,850 h^{-1}), whilst the di-Co(II) complex was slightly less active with a TOF of 200 h^{-1}. The catalysts were much more selective than their dizinc analogues, producing PCHC with no observable cyclic carbonate. The copolymer molecular weights were similar to those produced with zinc complex **22** ($<$10,000 g/mol with narrow PDI). Furthermore, a trimetallic cobalt(II) complex was synthesized but was even less active than its zinc analogue, producing short chain polymers (around 1,000 g/mol) with a TOF of 3 h^{-1} and 1 atm CO_2. The higher activity of the cobalt catalysts is believed to stem from the increased nucleophilicity of the cobalt–carbonate propagating species, as the rate-determining step is likely to be the epoxide ring opening by the nucleophilic carbonate chain, which would thereby be facilitated.

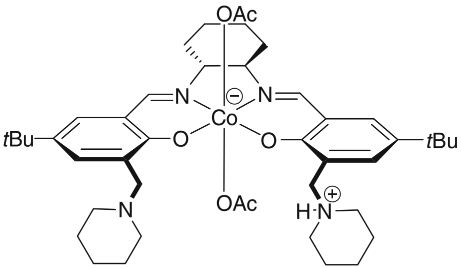
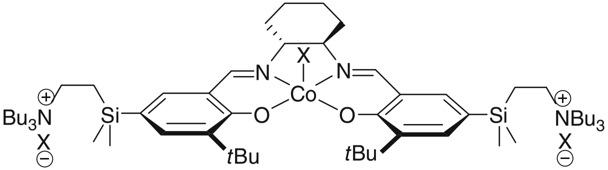
Finally, we reported a di-iron(III) catalyst **24** and the corresponding copolymerization activity [147]. This system was able to produce copolymer with CHO/CO_2 and demonstrated a TOF of 53 h^{-1}, at 80°C, 10 bar and a CHO/Fe ratio of 10,000:1. The system did not yield copolymer with PO, but addition of one equivalent of [PPN]Cl, per Fe centre, allowed the conversion of PO into cyclic propylene carbonate with TOFs around 10 h^{-1}. Previously, some heterobimetallic iron *tert*-butoxide complexes ($[(t\text{-BuO})_5FeLa]$ and $[(t\text{-BuO})_4FeZn]$) had been reported for the copolymerization of PO and CO_2 [153]. This catalyst was the first use of an iron complex for the homogeneous copolymerization of CHO and CO_2. Rieger and co-workers recently reported a mononuclear Fe system that showed similar behaviour towards PO [154] and some copolymer formation with CHO/CO_2 strongly dependent on the co-catalyst system [98].

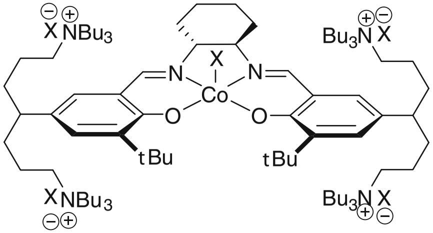
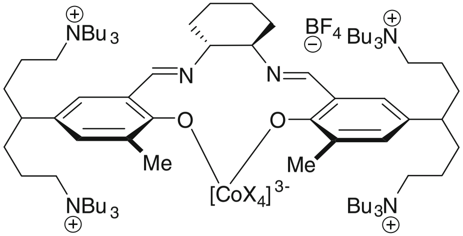
Table 7 Selected recent salen catalysts for epoxide/CO_2 copolymerization

Epoxide	Catalyst	T (°C)	$p[CO_2]$ (bar)	TON[a]	TOF[b]	% Carbonate[c]	Selectivity[c]	M_n[d]	PDI[d]	Reference
PO	 **25**	22	55	150	75	>92	>99	15,500	1.16	[155]
PO	 **26**	22	13.8	1,240	620	>98	>99	26,800	1.13	[155]

(continued)

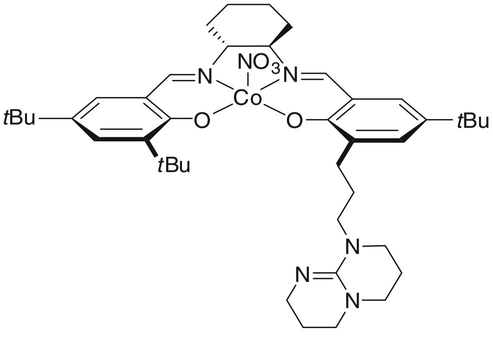
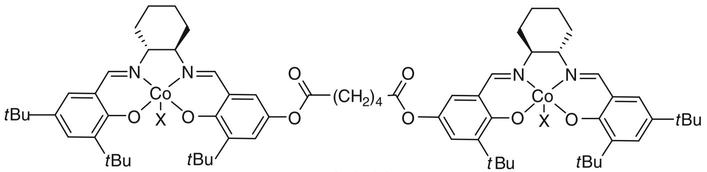
Table 7 (continued)

Epoxide	Catalyst	T (°C)	$p[CO_2]$ (bar)	TON[a]	TOF[b]	% Carbonate[c]	Selectivity[c]	M_n[d]	PDI[d]	Reference
PO	 **27**	60	14	680	680	>99	90	7,100	1.22	[156]
PO	 X = 2,4-Dinitrophenolate **28**	80	20	14,500	3,200	>99	84	53,000	1.35	[157]

PO	 X=2,4-Dinitrophenolate **29**	80	20	13,000	26,000	>99	84	38,000	1.34	[158]
PO	 X=2,4-dinitrophenolate **30**	70	20	2,500	1,300	>99	>99	208,000	1.20	[158]

(continued)

Table 7 (continued)

Epoxide	Catalyst	T (°C)	p[CO_2] (bar)	TON[a]	TOF[b]	% Carbonate[c]	Selectivity[c]	M_n[d]	PDI[d]	Reference
PO	 **31**	100	25	2,720	10,882	>99	97	60,200	1.23	[159]
PO	 X=O(O)CCF3 **32**	22	53	360	180	84	>99	36,700	1.07	[160]

[a] Moles epoxide consumed per metal
[b] Moles epoxide consumed per metal per hour
[c] Determined by ^{1}H NMR spectroscopy
[d] Determined by GPC using polystyrene standards

3.5 Salen Catalysts

Metal complexes coordinated by salen-type ligands are currently the most investigated homogeneous system for CO_2/epoxide copolymerization. An extensive review on [(salen)MX] catalyst systems was published by Donald Darensbourg in 2007, and the reader is referred to it [91]. Initial investigations focused on Cr complexes; however, recently [(salen)MX], catalysts have attracted much attention. Although the first generation of salen catalysts demonstrated lower activities ($\mathrm{TOF} = 160\ \mathrm{h}^{-1}$, $\mathrm{PPC} = 71\%$) than representative BDI-Zn catalysts, they were desirable for the high polymer selectivity, mild temperatures and pressures under which they operated. The first cobalt catalyst **25** (Fig. 23) was reported by Coates and co-workers in 2003 and produced PPC with 99% carbonate content with TOFs around 70 h^{-1} (Table 7) [136].

In addition to a different metal centre, simple changes to the axial group X of [(salen)MX] complexes have significantly increased activity and have drastically affected the copolymer/cyclic carbonate selectivity [155, 161]. For example, addition of sub-stoichiometric quantities of [PPN]Cl to complex [(salen)MX] **26** (where M = Co and X = pentafluorobenzoate) increased the activity substantially (TOFs of 620 h^{-1}) (Table 7) [155]. This also highlights the role of the co-catalyst: a range of nucleophilic and ionic species have been investigated. In general, the ideal ionic co-catalyst for high activities and selectivities consists of a bulky cation ($[\mathrm{PPN}]^+ > n\mathrm{Hept}_4\mathrm{N}^+ > n\mathrm{Bu}_4\mathrm{N}^+$) and a nucleophilic anion with poor leaving-group ability ($\mathrm{Cl}^- > \mathrm{Br}^- > \mathrm{I}^- > \mathrm{ClO}_4^-$). However, ionic species are also able to strongly coordinate to the metal centre, therefore competing with monomer/polymer coordination at the active site [162]. It is believed that co-catalysts are important in accelerating the catalysis by coordinating to the [(salen)MX] complex in a position trans to the X group, thereby forming a complex of the form [(salen)MX(Nu)]. However, an excess of the co-catalyst is detrimental for activity and selectivity towards the copolymer. It is proposed that at high co-catalyst loadings, the polymer chain end is in equilibrium with the co-catalyst and is detached from the metal centre, which promotes the formation of cyclic carbonate through backbiting.

Coates and Darensbourg have separately reported that salen metal catalysts undergo bimetallic initiation, followed by a monometallic propagation [123, 129, 155, 163]. In contrast, a theoretical study by Rieger and co-workers predicted chain growth to take place via the attack of the metal-bound alkyl carbonate on a metal-coordinated epoxide [103]. Related bimolecular processes have also been observed by Jacobsen et al. for the asymmetric ring opening of epoxides [164, 165]. Some of the mechanistic routes reported with metal salen catalysts are depicted in Fig. 24.

3.5.1 Binary Linked Salen Systems

As pointed out by several mechanistic studies, a binary or a dinuclear catalytic system is likely needed for CO_2/epoxide copolymerization with high activities.

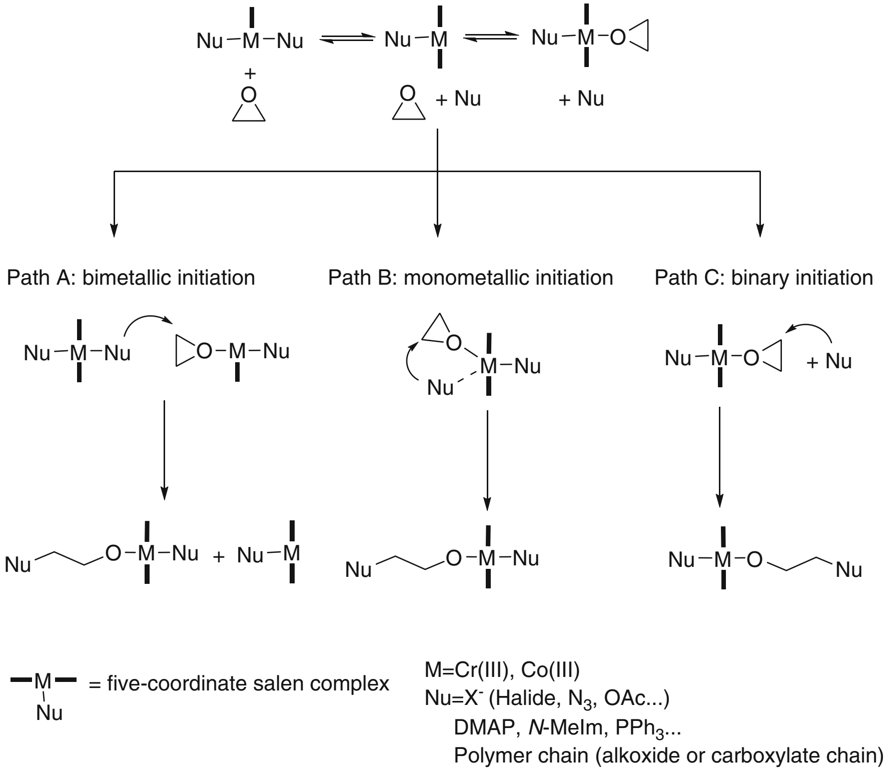
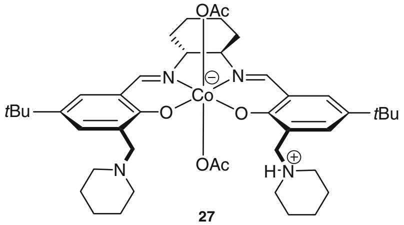


Fig. 24 Initiation mechanisms for a model salen complex: bimetallic pathway (**a**); monometallic pathway (**b**); binary pathway (**c**)



27

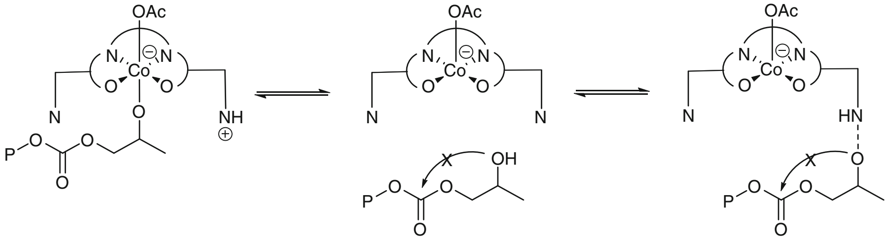
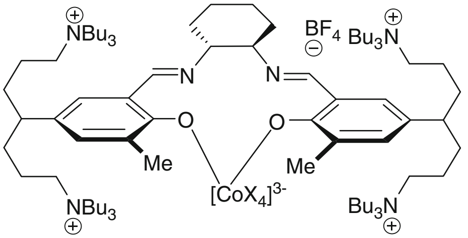


Fig. 25 Cobalt–salen complex **13** with cationic "arms" and proposed mechanism for prevention of cyclic formation



30

X=2,4-dinitrophenolate

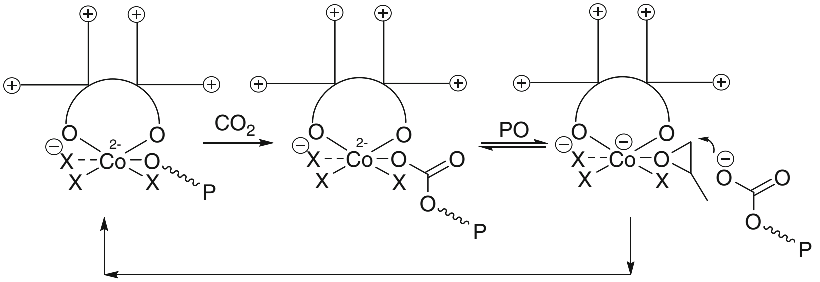


Fig. 26 Salen–Co(III) complex **30** with unusual bidentate ligand coordination mode and proposed copolymerization mechanism

In order to overcome the low activities typically observed at low catalyst concentrations, where all associative processes are disfavoured, some new strategies focused on tethering the co-catalyst to the salen ligand. In this way, even at high dilutions, the interacting species remain in close proximity, and these systems therefore retain their activity.

Thus, in 2006, Nozaki and her group reported a novel cobalt–salen catalyst **27** with two "side arms" bearing piperidine and piperidinium groups. The piperidinium substituent was proposed to prevent cyclic carbonate formation by protonating any copolymer chains that dissociated from the metal centre. The protonation of the chain end would reduce its nucleophilicity and hinder backbiting, thereby limiting cyclic carbonate formation. Using this single-component catalyst, the PO/catalyst ratio could be raised to 2,000:1, the temperature increased to 60°C, and high activities were maintained (TOF = 680 h^{-1}), with only 10% cyclic carbonate being produced [156] (Fig. 25).

This important new type of salen compound has led to the development of other single-component cobalt–salen catalysts, with co-catalyst substituents coordinated to the salen ligand, enabling further improvements in both activity and selectivity. Complex **28** (see Table 7) containing two tertiary ammonium groups showed excellent activity at low loadings and high temperatures (PO:**14** = 50,000) [157]. A TON of 14,500 and a TOF of 3,200 h^{-1} were reported at 80°C and 20 bar pressure, producing PPC with a high molecular weight of 53,000 g/mol and a PDI of 1.35.

Catalysts **29** and **30** also showed remarkable performances (Table 7). These cobalt–salen complexes feature a 2,4-dinitrophenolate (DNP) initiating group and 4-tributylammonium salts attached via four side chains. The catalysts copolymerized PO with a TOF of up to 26,000 h^{-1} and molecular weights approaching 300,000 g/mol and narrow PDI of 1.2 (although not under the same conditions) [158]. An interesting finding was that the catalyst could be recovered by flushing onto a silica gel then treatment with sodium 2,4-dinitrophenolate, and used again, albeit with lower activities. Based on multi-nuclear NMR and IR spectroscopies, DFT calculations and cyclic voltammetric (CV) studies, the authors later proposed that without a bulky *tert*-butyl group on the ligand, imine donors in salen-type ligand did not coordinate with cobalt. Instead, DNPs, which balanced the quaternary ammonium cationic arms, coordinated with cobalt creating a cobaltate complex with a formal triple negative charge on the metal [108, 166]. As a result, the usual tetradendate coordination of the salen ligand was changed into an unusual bidentate coordination mode (**30**, Fig. 26 and Table 7). It was proposed that the high activity observed with **30** (and derivatives) was due to "scrambling" of the anionic ligands; in particular, the cobaltate centre was shown to facilitate ligand substitution reactions by NMR spectroscopy. The proposed copolymerization mechanism involves dissociation of the anionic polymer chain, followed by epoxide coordination and ring opening by the anionic copolymer chain end; the latter is associated with the quaternary ammonium substituents (Fig. 26).

The coordination of Lewis bases, including tertiary amines, to the salen ligand was also investigated (Fig. 18) [159]. The attachment of an anchored triazabicyclodecene (TBD) group at the 2-position of one phenyl ring (vs. substituents at the 4-position for the previously prepared ammonium complexes) via a methylene or propylene link was achieved, as well as the addition of two TBD substituents via propylene linkages. Complex **31** (Table 7) was by far the most active of these complexes, converting PO to PPC with a TOF of 10,882 h^{-1} at a PO:**31** of 10,000:1, at 100°C and 25 bar CO_2. The copolymer selectivity was remarkably high at 97%, and this was proposed to be due to the ability of the pendant groups to stabilize the active Co(III) species against decomposition to an inactive Co(II) species. Complex **31** was also active under just 1 atm CO_2 pressure, giving an excellent TOF of 265 h^{-1}. Mechanistic studies using ESI mass spectrometry and in situ FT-IR spectroscopy suggested that the tethered TBD arm was capable of nucleophilic epoxide ring opening in an analogous manner to the DMAP and MTBD co-catalysts [135, 167], forming a tethered TBD-epoxide adduct (Fig. 27). Using this catalyst, the selective alternating copolymerization of CO_2 and styrene oxide to afford the corresponding polycarbonate with more than 99% carbonate linkages was achieved in 2010 by the groups of Lu and Darensbourg [168].

Catalysts with *N*-MeIm or quaternary ammonium substituents at the 2-position were also reported, but were either almost inactive (presumably because *N*-MeIm coordinates too strongly to the metal centre, inhibiting epoxide binding [162]) or of lower activity. However, the complex with a quaternary ammonium arm in the 2-position was later reported as an excellent catalyst for CHO copolymerization, under 1 atm pressure,

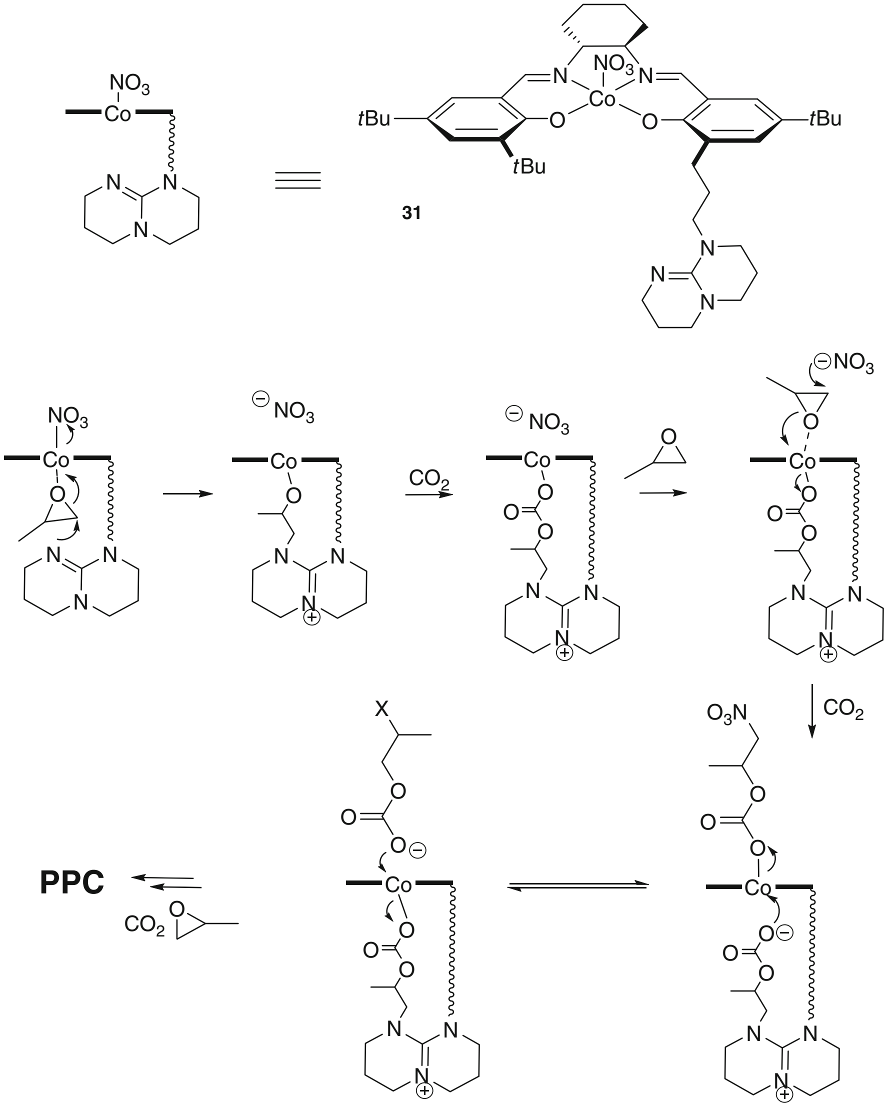
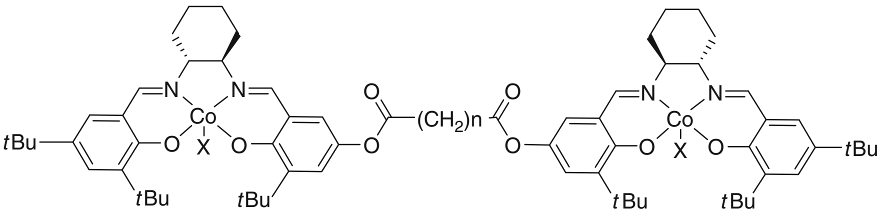


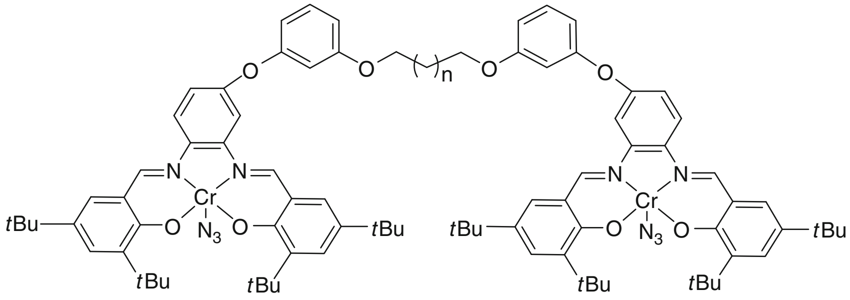
Fig. 27 Proposed copolymerization mechanism with complex **31**

giving a TOF of 263 h^{-1} at just 50°C, and producing a perfectly alternating high-molecular-weight copolymer ($M_n = 48{,}200$ g/mol, PDI $= 1.12$) [169].



X=O(O)CCF3, n=3, 4, 7 or 10

Fig. 28 Series of (*R*,*R*)–(*S*,*S*) dinuclear cobalt(III)–salen complexes synthesized by Nakano et al.



n=1,3 or 4

Fig. 29 Series of dinuclear chromium(III)–salen complexes synthesized by Vagin et al.

3.5.2 Binuclear Salen Systems

In 1998, the Jacobsen group reported that binuclear Cr(III)–salen catalysts showed greater activities (by one or two orders of magnitude) for the ring opening of epoxides [164, 170]. In 2010, Nozaki and co-workers further investigated this ligand system and synthesized a series of bimetallic Co(III)–salen complexes with different spacer lengths [160] (Fig. 28).

At a PO/Co ratio of 1000:1 (22°C, 53 bar), the racemic mononuclear catalyst showed comparable activity to the dinuclear systems (TOF between 100 and 180 h^{-1}); the dinuclear complexes only showed improved activities under high dilutions (lower catalyst loading). The most active complex was **32** ($n = 4$; see Table 4) which showed a TOF of 180 h^{-1} (PO/Co 3,000:1), and produced PPC with 84% carbonate linkages and a molecular weight of 36,700 g/mol (PDI = 1.07). This was markedly higher than the mononuclear analogue (TOF = 20 h^{-1}, under equivalent conditions) and also higher than analogues with longer bridge lengths. The finding that the activity of the mononuclear complexes decreased dramatically under high dilution conditions, yet the dinuclear analogue did not, indicated that the copolymerization proceeds via a dinuclear propagation mechanism. The addition of 0.5 equivalent of [PPN]Cl co-catalyst further increased the activity of the dinuclear system (max. TOF = 1,280 h^{-1}) as well as that of the mononuclear system (TOF = 1,180 h^{-1}). This indicated, as previously discussed by other authors, that in the presence of co-catalysts, a binary mechanism operates, which is independent of the nuclearity of the system. These data concur with the previously proposed mechanism by Coates and co-workers [171]. Concurrently, a related and independent study was reported by Vagin et al. [172]. Their new synthetic route allowed the preparation of dinuclear salen–Cr(III) complexes with different linker lengths (Fig. 29).

The same trend as that reported by the Nozaki group upon dilution was observed. The copolymerization conditions were 60°C and 40 bar CO_2, with a PO/Cr ratio of 20,000:1, the TOF of the optimal dinuclear complex was 82 h^{-1}, whereas the mononuclear analogue showed a TOF of just 7 h^{-1}.

4 Conclusions

The use of renewable resources in polymer synthesis and the use of inorganic and organometallic polymerization initiators and catalysts have been introduced. The ring-opening polymerization of lactide is an interesting method to prepare polylactide, a material applied in medicine and as a commodity polymer. The polymerization is initiated by a range of species, including metal complexes, enzymes and organocatalysts. Here, we have focussed on the application of complexes, particularly amido and alkoxide complexes, of group 3 and group 13 elements. The group 3 complexes show very fast rates of polymerization and, in some instances, good stereocontrol. Recent advances include the development of highly active, single-site initiators which have been useful probes for greater understanding of the coordination–insertion mechanism. An exciting development is the preparation of stereoblock polylactide (iso-selectivity) from *rac*-lactide using a racemic mixture of an yttrium complex. Such iso-selectivity from group 3 complexes is very interesting as it points to future developments to enable the preparation of both iso-selective and highly active initiators. The chemistry of group 13 has been dominated by the use of aluminium alkoxide initiators and by aluminium–salen complexes which show very high degrees of isotactic control in *rac*-lactide polymerization. Recently, the heavier congeners, Ga and In, have shown interesting initiator properties. One particularly promising development is the use of an initiating system comprising indium trichloride, base and alcohol which yields heterotactic PLA from *rac*-lactide. Future developments in the group 13 element chemistry are expected to include high degrees of stereoselectivity and improved understanding of the mechanism and faster rates of polymerization.

The review also addresses catalysts for the alternating copolymerization of carbon dioxide and epoxides. Although the process has been known for several decades, recently some interesting developments have led to more active and more selective catalysts. In particular, reports of catalysts able to operate under low (atmospheric) pressures of carbon dioxide could improve the feasibility of the process and present an interesting challenge in terms of understanding the catalytic activation of this notoriously stable molecule. A significant class of catalysts for CO_2/epoxide coupling are Co/Cr(III)–salen complexes which are most successful when applied with an ionic/Lewis base co-catalyst. Recently, there have been interesting developments in producing single-component catalysts incorporating the co-catalyst covalently attached to the salen ligand. A further advance has been the application of dinucleating salen ligands which leads to catalysts capable of operating under low loadings, thereby improving the TON/TOF and are useful tools for probing the polymerization mechanism. There are many opportunities for future development in this field, including the discovery of more ligands and metals capable of catalysis, detailed understanding of carbon dioxide activation, mechanistic insight for the copolymerization process and the production of materials with defined microstructures through regio-/stereoselective catalysis.

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