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Catalytic cleavage of vegetable oil derivatives to aldehydes and other bio-based building blocks

Duc Nam Vu

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Catalytic cleavage of vegetable oil derivatives to aldehydes and other bio-based building blocks

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ABBREVIATIONS

α -ketol	α -hydroxyketone	CVOs	Carbonated sunflower oil
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DIPEA	<i>N,N</i> -Diisopropylethylamine	DMAP	4-Dimethylaminopyridine
DMF	Dimethyl formamide	DMSO	Dimethyl sulfoxide
EVOs	Epoxidized vegetable oils	FAMEs	Fatty acid methyl esters
HAM	Hydroaminomethylation	HOSO	High-oleic sunflower oils
MOFs	Metal-Organic Frameworks	NBS	<i>N</i> -Bromosuccinimide
NHCs	<i>N</i> -Heterocyclic carbenes	NIPUs	Non-isocyanate polyurethanes
PDC	Dipicolinic acid	PLA	Polylactic acid
POM	Polyoxometalates	PPOM	Peroxopolyoxometallates
PTSA	<i>p</i> -Toluenesulfonic acid	PUs	Polyurethanes
PVC	Polyvinyl chloride	TBAB	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride	TBHP	<i>tert</i> -Butyl hydroperoxide
TFA	Trifluoroacetic acid	TGA	Thermogravimetric analysis
TK	Transketolase	TOF	Turnover frequency
TON	Turnover number	SET	Single-electron transfer

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GENERAL INTRODUCTION

“Make our planet great again” is an action message, not only from the French government but also from all the leaders over the world. But, anyone has a question surrounding their mind such as “Why we need to make it great again?”? Herein, we have an explanation for that question. In fact, the climate change caused many negative effects for our planet such as global warming, a rise of sea level or the decrease of biodiversity. This phenomenon could be explained by the the growth of world’s population, leading to a rapid increase of global demand of energy and materials. To deal with these issues, the use of renewable resources such as biomass which is abundant, cheap and with a low carbon emission, has become more important. Moreover, biomass can be produced in a sufficient volume for industrial purposes without compromising the human food supply. For example, the use of biomass represented 11% of total raw materials in German chemical industry in 2003 (Figure 1).¹ Although carbon-based products are mainly produced from crude oil but both crude oil and gas are not renewable resources and need a long-term process for their formations. Otherwise, the use of biomass is also a carbon neutral process because carbon dioxide (a major contributor of climate changes) could be captured during the growth of biomass through photosynthesis. Thus, sooner or later, biomass will replace fossil materials as a major feedstock for chemical production.

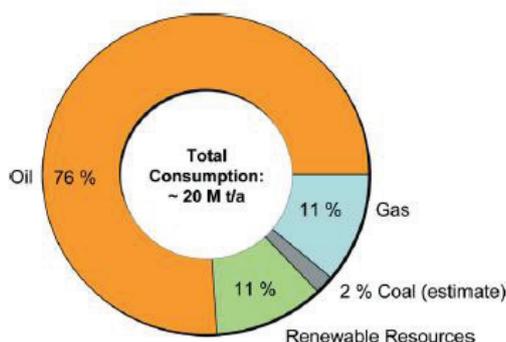


Figure 1: Use of raw materials in chemical industry in Germany, reprinted from ref 1.

In 1998, Paul Anastas and John Warner published a set of principles toward more sustainable approaches in Chemistry.² One of the key concepts in the frame of Green chemistry is use of renewable feedstocks in chemical production. For example, cellulose and hemicellulose are considered as a source of carbohydrates and phenolic derivatives could be released through depolymerization of lignin. Besides them, vegetable oils are also one of the most abundant chemical building blocks in nature. The main components of vegetable oils are triglyceride (a triester of glycerol and fatty acid) then vegetable oils could be converted to a variety of chemical platforms, from short chain (acetaldehyde, ethanol, lactic acid, etc) to long chain substrates (biodiesel, oligomers). Because of the potential applications of vegetable oils, “Picardie Innovation Végétales, Enseignements et Recherches Technologiques” (P.I.V.E.R.T) was created in 2011, within the frame of

¹ R. Diercks, J.-D. Arndt, S. Freyer, R. Geier, O. Machhammer, J. Schwartz, M. Volland, *Chem. Eng. Technol.* **2008**, *31*, 631–637.

² P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, **1998**, Oxford University Press, ISBN 9780198502340.

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French Institute for the Energy Transition and was selected as an investment for the future. The main target of this framework is to create a biorefinery from vegetable oil and the valorization of all plants. In fact, at the beginning, proteins and bio-diesel were the most valuable products from vegetable oils. However, a political rule was recently proposed by the French government and is limiting the application of biodiesel.³ In order to valorize vegetable oils, they should be converted to other value-added products such as surfactants, polymers and chemists have much to contribute to solve these challenges.

Nowadays, the use of renewable resources has become a great interest in industrial chemistry because it could reduce the addiction on fossil materials and decrease the emission of greenhouse gases. In this context, vegetable oils and animal fats are promising renewable feedstocks that are cheap and widely available. In 2009, the world's production of vegetable oils accounted for 137 million tons (Mt) and increased to 185 Mt in 2016 (an increase of 35%).⁴⁻⁵ Among them, the four most produced oils are Palm oil, Soybean oil, Rapeseed oil and Sunflower oil that represent 87% of the global production. The remaining oils consist of a variety of plant oils such as Olive oil, Linseed oil, Castor oil, Cotton seed oil, etc.

There are two major consumptions of plant oils and animal fats. On the one hand, the use of vegetable oils for culinary purpose represents approximately 80% of the global production. On the other hand, 20% of the world's production is currently used for industrial applications (Scheme 2). For instance, fatty acid methyl esters (FAMES) that are produced from the transesterification of vegetable oils, are considered as bio-fuels for transports.⁶ In 2017, the global production of bio-diesel was forecasted to approximately 34.5 billion liters with a cheap price, estimately around 75 euros per hectalitre.⁷ Among them, 19.9 billion liters are produced from developed countries and 14.5 billion liters are obtained from developing countries with the two biggest producers of the palm oil diesel from Malaysia and Indonesia.

Vegetable oil derivatives could be also used for the preparation of polymers or surfactants, *e.g.* castor oil that is consisting in at least 85% of ricinoleic acid, could be used as polyols in the production of polyurethane foaming.⁸ Lauric acid, that is a major fatty acid of coconut oil, is used in the production of ionic surfactants such as sodium dodecyl sulfate. Other important intermediates of plant oils are epoxidized vegetable oils. Firstly, they can be used directly as stabilizers in the production of PVC or as plasticizers for other plastics. Secondly, they could be functionalized to other

³ https://www.lemonde.fr/planete/article/2017/07/06/nicolas-hulot-annonce-une-prime-pour-replacer-les-vehicules-les-plus-polluants_5156706_3244.html, retrieved in August 2018.

⁴ U. Biermann, U. Bornscheuer, M. A. R. Meier, J. O. Metzger, H. J. Schafer, *Angew. Chem. Int. Ed.* **2011**, *50*, 3854 – 3871.

⁵ <http://www.biofuelsdigest.com/bdigest/2016/09/25/global-201617-vegetable-oil-production-to-hit-record-level-usda/>, retrieved in July 2018.

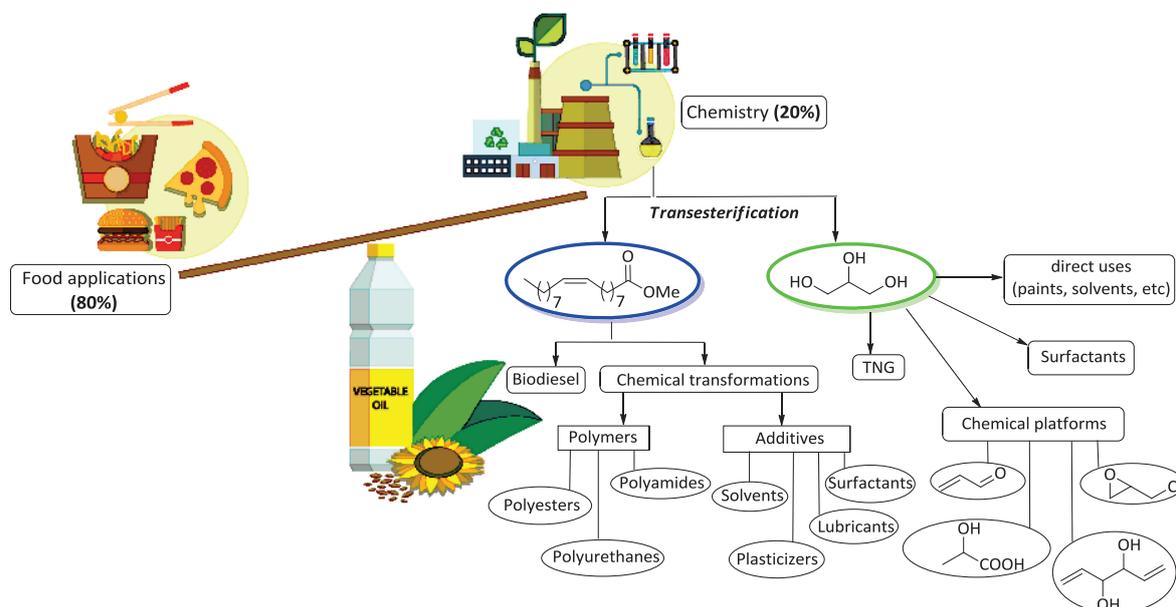
⁶ A. Esipovicha, S. Danova, A. Belousova, A. Rogozhina, *J. Mol. Catal A Chem* **2014**, *395*, 225–233.

⁷ OECD/FAO (2016), "Biofuels", in OECD-FAO Agricultural Outlook 2016-2025, DOI: dx.doi.org/10.1787/agr-outl-data-en.

⁸ T. Gurunathan, S. Mohanty, S. K. Nayaka, *Prog. Org. Coat.* **2015**, *80*, 39–48.

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interesting chemical platforms such as diols for the synthesis of polyurethanes, diacyl substrates for bio-lubricants, cyclic carbonates for the bio-based solvents or non-isocyanate polyurethanes, etc.^{9,10} Glycerol that is a co-product of the transesterification of plant oils, is also an interesting chemical platform in fine chemistry.¹¹ It should be noted that the production of each 10 kg of biodiesel *via* transesterification process yields approximately 1 kg of crude glycerol. Firstly, glycerol is directly used as an important excipient in the formulation of medicine or as humectants and moisteners in many skin and hair care products. Secondly, it could be easily converted to other useful substrates. Historically, trinitroglycerin was employed in the production of propellants. Later, this derivative was also used as a potent vasodilator to treat heart conditions such as angina pectoris and chronic heart failure. Moreover, glycerol is considered as key bio-based feedstock for the synthesis of 1,2-propanediol, acrolein, glycerol carbonate and glycerol ethers that have a variety of applications in the preparation of polyurethanes or bio-surfactants.^{11,12,13}



Scheme 1: Some applications of vegetable oil derivatives

Aldehydes are important chemicals in organic synthesis, due to their wide applications in cosmetics, pharmaceuticals and herbicides. Moreover, they can be converted to value-added compounds such as surfactants, polymers, etc. Traditionally, aldehydes are mainly obtained through oxo-process by hydroformylation of olefins or reductive ozonolysis of alkenes.¹⁴ Next to them, the reduction of fatty acids or the dehydrogenation of primary alcohols were used in several cases to prepare some aldehydes.¹⁴ However, both methods suffer from their drawbacks such as the price of

⁹ S. M. Danov, O. A. Kazantsev, A. L. Esipovich, A. S. Belousov, A. E. Rogozhin, E. A. Kanakov, *Catal. Sci. Technol.* **2017**, *7*, 3659–3675.

¹⁰ Y. Li, X. Luo, S. Hu, Bio-based Polyols and Polyurethanes, **2015**, DOI: 10.1007/978-3-319-21539-6_2.

¹¹ H.W. Tan, A.R. Abdul Aziz, M.K. Aroua, *Renew. Sust. Energ. Rev.* **2013**, *27*, 118–127.

¹² A. Brandner, K. Lehnert, A. Bienholz, M. Lucas, P. Claus, *Top Catal* **2009**, *52*, 278–287.

¹³ M. Sutter, E. Da Silva, N. Duguet, Y. Raoul, E. Metay, M. Lemaire, *Chem. Rev.* **2015**, *115*, 8609–8651.

¹⁴ M. Eckert, G. Fleischmann, R. Jira, H. M. Bolt, K. Golka, *Ullmann's Encyclopedia of Industrial Chemistry*, *1*, *acetaldehydes*, DOI: 10.1002/14356007.a01_031.pub2.

GENERAL INTRODUCTION

catalyst or the requirement of special equipment. Consequently, the development of greener approaches for the production of aldehydes is highly desirable. The project WP3P21-BIOALDEHYDES was financed by PIVERT in 2015 through GENESYS programme for the cleavage of vegetable oil derivative to prepare aldehydes and to valorize these products in polymer. This work was carried out in collaboration between Institute Chemistry, Biochemistry and Supramolecular Chemistry (team CASYEN) and Institute Charles Gerhardt Montpellier (team IAM) from 2015 to 2018.

In this manuscript, our work will be presented in 5 chapters:

Chapter 1: An overview of the literature on vegetable oils will be given, including the important chemical transformations of vegetable oil as well as the use of organocatalysts to convert these materials.

Chapter 2 and 3: A first method to approach bio-aldehydes is presented. Two homogeneous and heterogeneous catalytic metal-based methods to prepare fatty α -hydroxyketones from oleochemical 1,2-diols have been described. Then, the cleavage of these fatty substrates has been studied, through organocatalyst. Moreover, the valorization of aldehydes was also investigated through a Stetter reactive to give bifunctional derivatives that could be used as monomers.

Chapter 4: The cleavage of fatty diketones is studied by organocatalysis to give the two corresponding esters which could also serve as monomers.

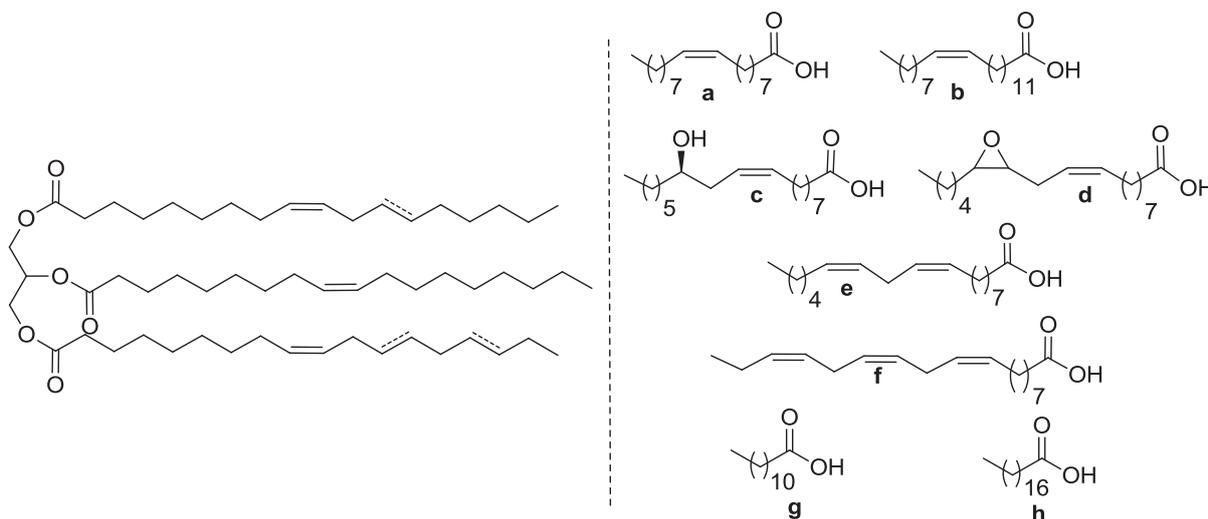
Chapter 5: A second method to obtain aldehydes from fatty substrates has been described through a two-step synthesis. The first step is a nucleophilic addition of H_2O_2 on fatty epoxide to provide fatty β -hydroxy hydroperoxide and the second one involves the decomposition of this species under thermal conditions.

Then, a general conclusion will be given to summarize all the results of this thesis and several perspectives will be proposed for future work.

Finally, experimental data will be presented in the last section of this manuscript, including all the experimental procedures and NMR characterizations of all products.

1. Vegetable Oils- Structure, composition

Vegetable oils (VO or triglycerides) are a combination of glycerol and three moieties of (un)saturated fatty acids that have between 12 and 22 carbons in the fatty chain with 0 to 5 double(s) bond(s) per fatty acid. Among them, there are some common fatty acids that are usually encountered in plant oils (Scheme 2).



Scheme 2: (Left) A typical structure of vegetable oils; (Right) Some common fatty acids in VOs: a) Oleic acid, b) Erucic acid, c) Ricinoleic acid, d) Vernolic acid, e) Linoleic acid, f) α -linolenic acid, g) Lauric acid, h) Stearic acid.

2. Functionalization of vegetable oils

There are plenty of transformations of vegetable oils that could convert triglycerides to valuable compounds. For example, the reaction on the carbonyl group could provide a series of interesting bio-based platforms bearing different functional groups such as alcohols, amines, amides or nitriles. The reaction on the hydrocarbon chain could also give another family of value-added substrates. However, in this context, we would like to focus on some transformations of interest that are the most studied such as epoxidation (plasticizers), dihydroxylation (hyperbranched polyester), ozonolysis (fatty acids/aldehydes) or metathesis (polyamides). All of these functionalizations are focused on the unsaturated vegetable oil derivatives and the method described will be presented on vegetable oils but they could be also applied to fatty acids or esters, using oleic moiety as a model unsaturated fatty derivative.

2.1 Epoxidation

Epoxidized vegetable oils are one of the major functionalized derivatives of triglycerides due to their wide variety of applications such as plasticizers, lubricants, paints and dyes formulation. Furthermore, they are considered as an interesting intermediate for preparation of value-added compounds such as diols, cyclic carbonates, monoketone derivatives, etc. In 2013, the industrial

production of epoxidized vegetable oils reached about 200,000 metric tons.¹⁵ Herein, the main methods for preparation of epoxidized triglycerides will be summarized and several perspectives will be presented.

2.1.1 Homogeneous catalytic systems

There are a lot of methods described for the synthesis of oleochemical epoxides from unsaturated vegetable oils. One of the most efficient pathways is to use peracids as oxidants. However, almost all peracids are not really stable. That is the reason why a mixture of H₂O₂ and an organic acid is generally used to generate *in situ* the peracid. Indeed, this process includes three steps: i) *in situ* formation of the peracid by oxidation of the acid in the presence of hydrogen peroxide and transfer of the peracid from aqueous phase to organic phase; ii) oxidation of the olefin derivative to epoxide by the peracid then, iii) re-oxidization of the acid to the peracid. Furthermore, a catalytic amount of strong inorganic acids (H₂SO₄, HCl, H₃PO₄ or HNO₃) could be necessary to increase the kinetics of formation of the peracid. The reaction is often performed at moderate temperature (40-60°C for HCOOH or 60-80°C for CH₃COOH) and usually requires an excess of hydrogen peroxide. It should be noted that hydrogen peroxide is considered as a green, cheap and efficient oxidant¹⁶ because it has the highest content of active oxygen of all common oxidants (Table 1) and only water is a co-product.

Table 1: Active oxygen contained in common oxidants

Entry	Oxidant	Active oxygen content (%)	Co-product
1 ^a	H ₂ O ₂	47.1	H ₂ O
2	O ₃	33.3	O ₂
3	NaClO	21.6	NaCl
4	NaBrO	13.4	NaBr
5	<i>t</i> -BuOOH	17.8	<i>t</i> -BuOH
6	<i>m</i> -CPBA	9.3	<i>m</i> -CBA
7	Urea.H ₂ O ₂	17.0	Urea, H ₂ O
8 ^b	NaIO ₄	7.2	NaIO ₃
9	KHSO ₅ (Oxone [®])	10.5	KHSO ₄

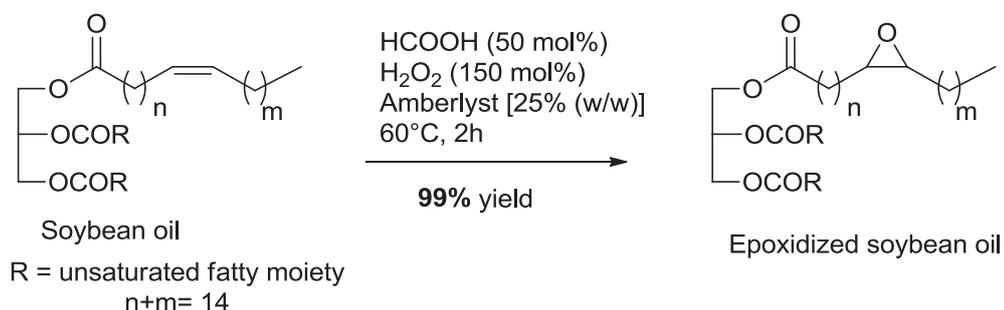
^acalculated on 100% H₂O₂; ^bassuming only one oxygen atom is utilized; *m*-CPBA = meta-chloroperbenzoic acid, *m*-CBA = meta-chlorobenzoic acid.

¹⁵ J. M. Fraile, J. I. García, C. I. Herrerías, E. Pires, *Synthesis* **2017**, 49, 1444–1460.

¹⁶ R. Noyori, M. Aokib, K. Satoc, *Chem. Commun.* **2003**, 1977–1986.

CHAPTER I: VEGETABLE OIL

According to Lewandowski *et al*, the epoxidation of rapeseed oil was carried out using an homogeneous system $\text{AcOH}/\text{H}_2\text{O}_2$ in the presence of small amount of H_2SO_4 . The reaction was performed at 65°C for 6 hours and provided the desired products with 66% yield.¹⁷ In the literature, several organic acids were also used such as HCOOH , CH_3COOH and benzoic acid. However, considering the cost and the work-up, performic and peracetic acids were usually preferred for preparation of the epoxidized vegetable oils (EVO). A comparison of the efficiency of different acids showed that performic acid is the most suitable reagent for this transformation.¹⁸ For example, an excellent yield (99%) was achieved when soybean oil was epoxidized by a mixture of $\text{H}_2\text{O}_2/\text{HCOOH}$ in the presence of Amberlyst at 60°C for 2 hours (Scheme 3).

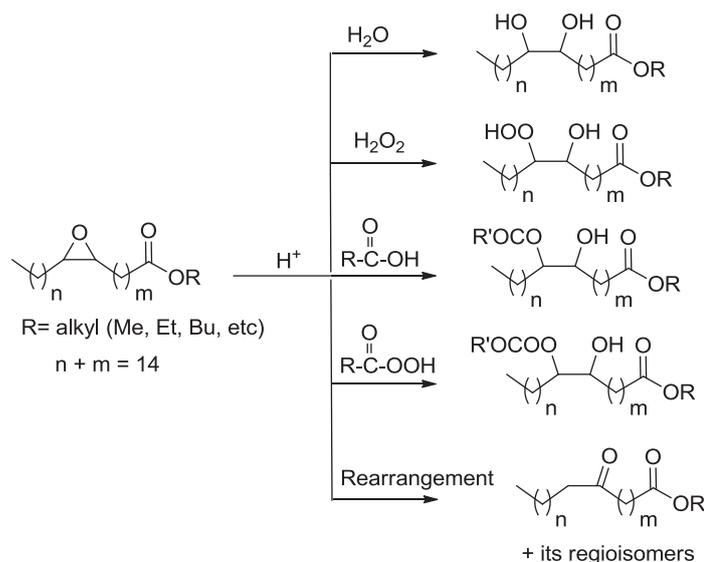


Scheme 3: Preparation of epoxidized soybean oil

The activation energy for epoxidation process of fatty acid derivatives was also determined. The value of the activation energy for peroxyacetic acid (54.7 ± 2.1 kJ/mol) is higher than that for peroxyformic acid (35.9 ± 5.2 kJ/mol), indicating that the epoxidation with performic acid is easier than with peracetic acid. However, these conventional epoxidation methods suffer from several disadvantages. Firstly, a series of side reactions could be produced, especially through ring-opening of oxiranes, leading to a decrease of the yield of the desired products, (Scheme 4). Secondly, the epoxidation is a highly exothermic reaction. It could present a risk when the reaction is performed in the presence of corrosive agents such hydrogen peroxide and peracid. Thirdly, the use of a catalytic amount of inorganic acids (except solid Lewis acids) in particular sulfuric acid, generates a large amount of non-recyclable wastes.

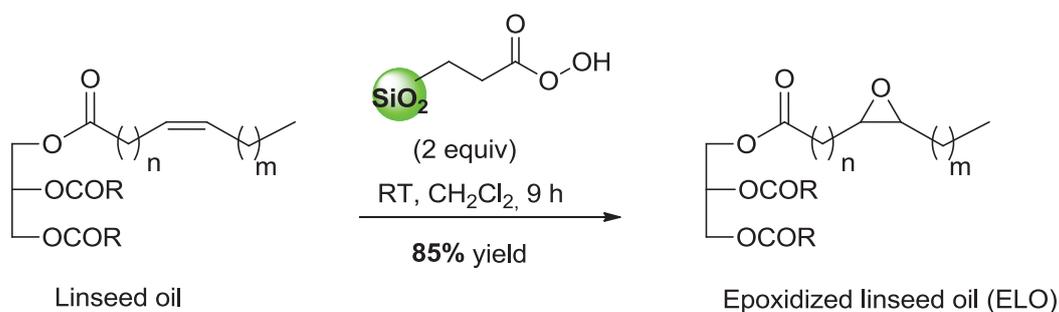
¹⁷ E. Milchert, A. Smagowicz and G. Lewandowski, *J. Chem. Technol. Biotechnol.*, **2010**, *85*, 1099–1107.

¹⁸ Z. S. Petrović, A. Zlatanić, C. C. Lava and S. Sinadinović-Fišer, *Eur. J. Lipid Sci. Technol.*, **2002**, *104*, 293–299.



Scheme 4: Potential side-reactions from the epoxidation of unsaturated fatty acid derivatives

A supported version of peracid was reported by Pan *et al.*¹⁹ A peroxy-carboxylic acid was immobilized on the surface of silica, then this oxidant was used for the epoxidation of vegetable oils at room temperature (Scheme 5). After 9 hours, the epoxidation of linseed oil was complete with 85% yield. The major by-products obtained are monoketone derivatives because silica is acidic and could play the role of a Bronsted acid catalyst and promote a Meinwald rearrangement.²⁰ The regeneration of peracid was done using a mixture of hydrogen peroxide and a catalytic amount of sulfuric acid. Moreover, the oxidant could be easily separated, regenerated and recycled at least 5 times without any loss of activity.



Scheme 5: Epoxidation of linseed oil by peracid supported on silica

An alternative pathway to replace the direct use of peracid was studied using a mixture of metal and hydrogen peroxide (H_2O_2). According to Gerbase *et al.*, the epoxidation of soybean oil was optimized in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}_2$ biphasic system, using a catalytic amount of methyltrioxorhenium (CH_3ReO_3). The reaction was performed at room temperature and

¹⁹ M.-Y. Yao, Y.-B. Huang, X. Niu, H. Pan, *ACS Sustainable Chem. Eng.* **2016**, *4*, 3840–3849.

²⁰ J. Meinwald, S.S. Labana, M.S. Chadha. *J. Am. Chem. Soc.* **1963**, *85*, 582–585.

provided 95% of epoxidized products after only 2 hours.²¹ A similar work was also reported by Marks and Larock.²² In the presence of methyltrioxorhenium (0.34 mol%), pyridine (8.15 mol%) and hydrogen peroxide (1.0 equiv) in CH₂Cl₂ at 25°C, the epoxidation of Norway fish oil ethyl ester was complete and gave 86% yield of the desired products after 6 hours. However, the rhenium-based catalyst is expensive and not easy to recycle. Furthermore, the purification was difficult and the use of an external base led to a low atom-economy and the process is not easy to upscale.

Along with peracid and hydrogen peroxide, a series of oxidizing agents was employed in the epoxidation of vegetable oil derivatives such as *t*-butyl hydrogen peroxide (*t*-BuOOH),²³⁻²⁴ oxone²⁵ or oxygen/aldehyde.²⁶ Although these epoxidation reactions provided good yields (up to 99%), most of these methods suffer from the use of metal catalyst (such Mo, V, etc) or toxic solvents (CH₂Cl₂, C₂H₄Cl₂) and finally can not replace the conventional epoxidation using mineral acid and hydrogen peroxide.

2.1.2 Polyoxometalates

Polyoxometalates (POM) are a class of anionic metal oxide in group V and VI. They are constructed through the condensation of metal oxide polyhedral (MO_x, M= Mo, W, Nb, V, etc x= 4-7) with each other in the corner or edge. POMs are used as precursors of highly efficient catalysts for environmentally-friendly biphasic epoxidation with hydrogen peroxide. In the presence of an oxidant such H₂O₂, POM are converted to peroxopolyoxometalates (PPOM) which are active species for the epoxidation of triglyceride derivatives. PPOMs are often used with quaternary ammonium salts as phase transfer catalysts to increase the solubility of the substrates and facilitate the regeneration of PPOM.

There are six different types of POMs and PPOM, including Keggin, Dawson, Anderson, Lindqvist, Waugh and Silverton, in which Keggin-type structure, that has tetrahedrally-coordinated heteroatom, is the most stable one among various complexes (Figure 2).²⁷

²¹ A. E. Gerbase, J. R. Gregório, M. Martinelli, M. C. Brasil, A. N. F. Mendes, *J. Am. Oil Chem. Soc* **2002**, 79, 179-181.

²² D. W. Marks and R. C. Larock, *J. Am. Oil Chem. Soc.* **2002**, 79, 65–68.

²³ M. M. Cecchini, F. De Angelis, C. Lacobucci, S. Reale, M. Crucianelli, *Appl. Catal., A.* **2016**, 517, 120-128.

²⁴ Y. Kuwahara, N. Furuichi, H. Sekic, H. Yamashita, *J. Mater.Chem. A* **2017**, 5, 18518–18526.

²⁵ D. Yang, Y.-C. Yip, G.-S. Jiao, M.-K. Wong, *J. Org. Chem.* **1998**, 63, 8952-8956.

²⁶ L. Vanoye, Z. E. Hamami, J. Wang, C. de Bellefon, P. Fongarland, A. Favre-Reguillon, *Eur. J. Lipid Sci. Technol.* **2017**, 119, 1600281.

²⁷ S. Omwoma, C. T. Gore, Y. Ji, C. Hu, Y.-F. Song, *Coord. Chem. Rev.* **2015**, 286, 17–29.

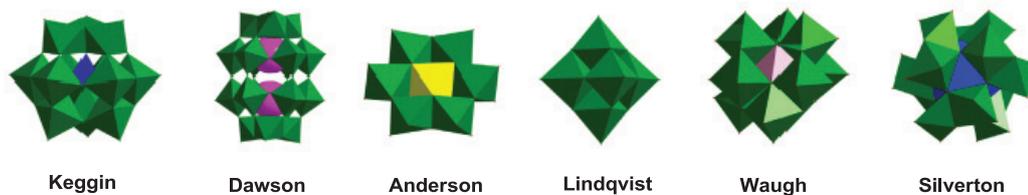


Figure 2: Classical POMs structures in polyhedral representations. Reprinted from ref 10.

The first report using POM for epoxidation of petrol-based olefins such as 1-dodecene, 1-octene, styrene or cyclohexene was studied by Venturello *et al* in 1983.²⁸ In the presence of POMs based on W or Mo (1 mol%) in acidic medium, a quantitative conversion of hydrogen peroxide was obtained and approximately 80% of epoxidized derivatives were isolated after a short-time period (1-3 hours).

There are a lot of researches to identify what species is the real “active” species for epoxidation of vegetable oils. They found that PPOM complexes play a crucial role for this transformation. Some of them were reported, in particularly Venturello’s anion ($\{PO_4[WO(O_2)_2]\}^{3-}$),²⁸ Ishii’s anion ($[PW_{12}O_{40}]^{3-}$)²⁹ and Mizuno’s anion ($[W_2O_3(O_2)_4]^{2-}$)³⁰⁻³¹ (Figure 3).

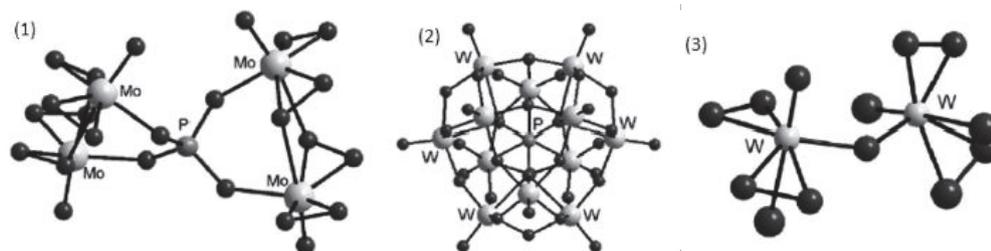


Figure 3: Schematic structures of PPOM anions: 1) ($\{PO_4[WO(O_2)_2]\}^{3-}$), 2) ($[PW_{12}O_{40}]^{3-}$), 3) ($[W_2O_3(O_2)_4]^{2-}$). Reprinted from ref 14.

PPOM often exist as a salt in the combination with quaternary ammonium such tetra-(*n*-butyl) ammonium, methyltriocetyl ammonium or $[\pi-C_5H_5N-(CH_2)_{15}CH_3]^+$ and receive a lot of attention for selective epoxidation of vegetable oils. For example, the epoxidation of soybean oil using $[\pi-C_5H_5N-(CH_2)_{15}CH_3][PW_4O_{16}]$ as a catalyst, was complete after 3-4 hours and 90% of the desired products were obtained (Scheme 6).³²

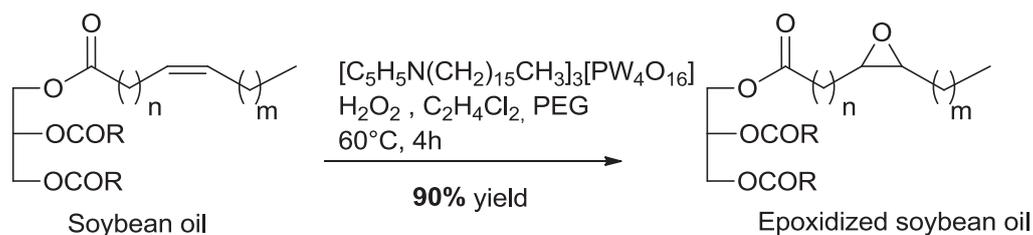
²⁸ C. Venturello, E. Alneri, M. Ricci, *J. Org. Chem.* **1983**, *48*, 3831-3833.

²⁹ Y. Ishii, K. Yamawaki, T. Ura, H. Yamada, T. Yoshida, M. Ogawa, *J. Org. Chem.* **1988**, *53*, 3587–3593.

³⁰ K. Kamata, S. Kuzuya, K. Uehara, S. Yamaguchi, N. Mizuno, *Inorg. Chem.* **2007**, *46*, 3768–3774.

³¹ Z. P. Pai, D. I. Kochubey, P. V. Berdnikova, V. V. Kanazhevskiy, I. Y. Prikhod'ko, Y. A. Chesalov, *J. Mol. Catal. Chem.* **2010**, *332*, 122–127.

³² W. Cheng, G. Liu, X. Wang, X. Liu, L. Jing, *Eur. J. Lipid Sci. Technol.* **2015**, *117*, 1185–1191.



Scheme 6: Biphasic epoxidation of soybean oil catalyzed by polyoxotungstates

However, these catalytic systems could be unstable. According to Leng *et al*, the selective epoxidation of soybean oils using PPOM gave 97% conversion and 82% selectivity after the first run.³³ However, for the next three cycles, the conversion and selectivity declined significantly to 24% and 20%, respectively. The authors explained these results by FT-IR-analysis of the spent catalyst. The disappearance of the peak at 850 cm^{-1} , corresponding to the signal of Venturello-Ishii's anion, indicated that the loss of the active site PPOM could be responsible for the decrease of the catalytic performances.

In order to improve the stability and recyclability of the catalysts, POM were immobilized onto several supports. These supports could be organic such as resins³⁴ or inorganic such silica³⁵ or palygorskite.³⁶ The supported version of PPOM was used for epoxidation and was easily separated by filtration. It was also described that PPOM have a good stability on the immobilized materials and the catalysts could be reused without loss of activity.

2.1.3 Enzymatic epoxidation

Enzymatic catalysis is an interesting pathway to access epoxidized vegetable oils with many advantages such as high conversion, good regio- and stereoselectivity, especially not giving any unwanted epoxide ring-opening products. The enzymatic epoxidation is often performed in tri-phasic media where H_2O_2 is in water phase, vegetable oils are in the organic phase (if necessary) and a solid catalyst containing the immobilized lipase, usually *Candida antarctica* lipase B (CALB) supported onto acrylic resin (Novozym® 435)³⁷⁻³⁸ or silica (CALB-silica).³⁹ However, the mechanism of enzymatic epoxidation is specific and quite different in comparison with traditional epoxidation processes (Scheme 7). Firstly, perhydrolysis of vegetable oils was performed in the presence of lipase and hydrogen peroxide to give perfatty acid derivatives. Secondly, the perfatty acid can oxidize the olefin derivatives to provide EVO and corresponding fatty acid. Then, this acid was re-oxidized to peracid by

³³ J. Wu, P. Jiang, X. Qin, Y. Ye, Y. Leng, *Bull. Korean Chem. Soc.* **2014**, *35*, 1675–1680.

³⁴ E. Poli, J.-M. Clacens, Y. Pouilloux, *Catal. Today* **2011**, *164*, 429–435.

³⁵ E. Poli, R. De Sousa, F. Jerome, Y. Pouilloux, J.-M. Clacens, *Catal. Sci. Technol.* **2012**, *2*, 910–914.

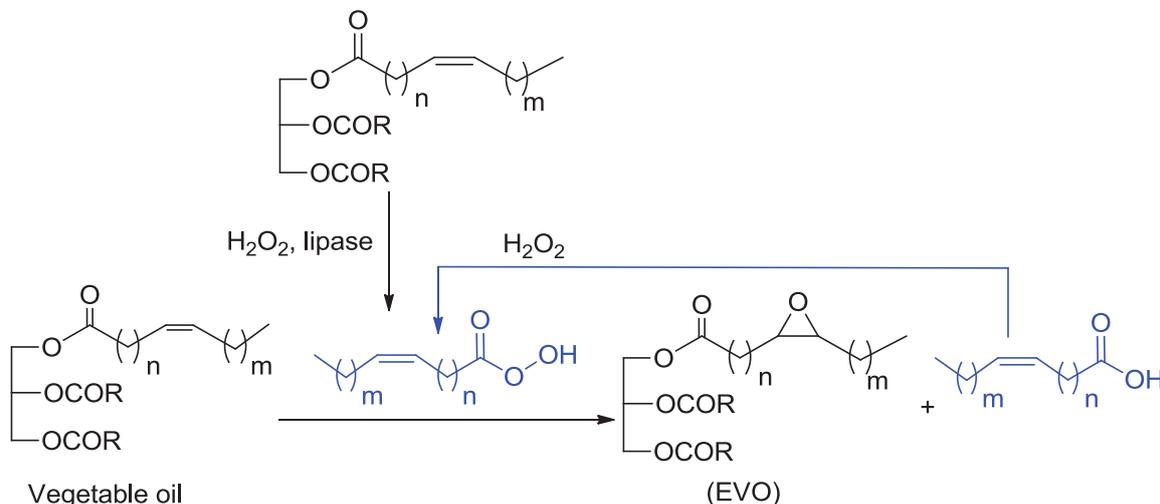
³⁶ H. Zhang, H. Yang, H. Guo, J. Yang, L. Xiong, C. Huang, X. Chen, L. Ma, Y. Chen, *Appl. Clay Sci.* **2014**, *90*, 175-180.

³⁷ T. Vlček, Z. S. Petrović, *J. Am. Oil Chem. Soc.* **2006**, *83*, 247–252.

³⁸ M. Rüschen Klaas, S. Warwel, *Ind. Crops Prod.* **1999**, *9*, 125–132.

³⁹ L. A. Rios, D. A. Echeverri, A. Franco, *Appl. Catal., A.* **2011**, *394*, 132–137.

action of hydrogen peroxide. Finally, at the end of reaction, the epoxy products were a mixture containing the mono-, di- and triglycerides products. To improve this method, a catalytic amount of organic acid (<5 mol%) such acetic acid was added to form the active species (peroxyacid) and avoid the hydrolytic activity.^{15,40}



Scheme 7: Enzymatic epoxidation of vegetable oils

However, enzymatic epoxidation of vegetable oils showed a lower activity in comparison with chemical epoxidation process of free fatty acids or fatty acid methyl esters (FAMES). It could be explained by the steric hindrance of triglycerides, leading to less interaction between active sites and plant oils. Moreover, the catalyst seems to be easily decomposed. In an investigation by Rios *et al.*, epoxidation of methyl ester derived from jatropha oil using CALB-silica provided an excellent conversion (*ca* 100%) and selectivity (*ca* 100%) after 24 hours.³⁹ However, the catalyst completely deactivates after 1 cycle. The reasons for the decomposition of lipase might be the high temperature or high concentration of hydrogen peroxide. Finally, although obtaining good advantages in the view of selectivity and mild condition, enzymatic epoxidation has also several drawbacks such as a large excess of solvents is required, low conversion toward triglycerides, quick decomposition and high cost of lipases. Improving all of these points, the enzymatic epoxidation will get a chance to compete with the conventional epoxidation routes.

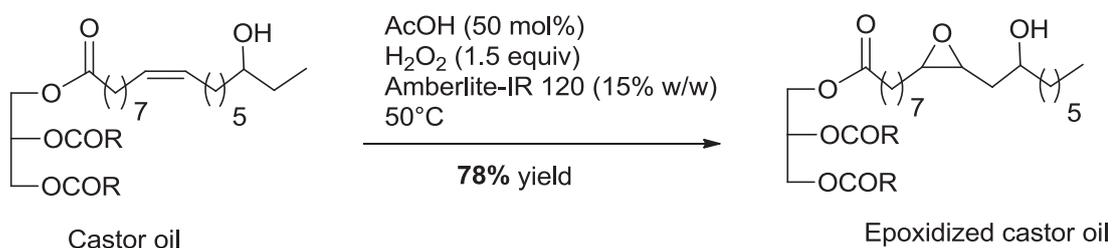
2.1.4 Heterogeneous catalytic system

In order to obtain an environmentally-friendly epoxidation and avoid the drawbacks of homogeneous catalytic systems, the development of novel heterogenous system received more and more attentions. Solid Lewis acids and Ti-based catalysts are commonly used as the heterogenized catalysts for the epoxidation of fatty acid derivatives.

⁴⁰ E. Milchert, K. Malarczyk, M. Klos, *Molecules* **2015**, *20*, 21481–21493.

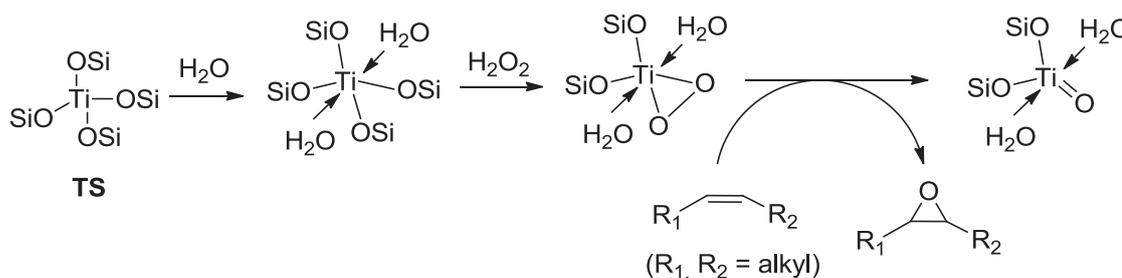
CHAPTER I: VEGETABLE OIL

Solid Bronsted acids, most often acidic ion-exchange resins such Amberlite®, Nafion® or Aquivion®, are substitutes for strong mineral acids in the conventional homogeneous epoxidation. They are functionalized polymers that could provide the acidic sites in the solid medium and resist at high temperature (ordinary between 120-170°C). Moreover, they could be easily separated and recycled after epoxidation process. According to Fišer *et al*,⁴¹ the epoxidation of castor oil in the catalytic system of AcOH/H₂O₂/Amberlite IR-120 provided 78% yield of desired products (Scheme 8). Moreover, the solid Bronsted acid could be recycled at least 4 times without losing any activity.⁴² Unfortunately, approximately 15-20% (w/w substrates) of solid Bronsted acid is often required for this kind of transformation, that could restrict the application of acid resins in large-scale epoxidation process.



Scheme 8: Epoxidation of castor oil using Amberlite IR-120

More recently, Ti-based catalysts, in particular titanium silicates, are one of the best candidates for heterogeneous epoxidation of vegetable oils with hydrogen peroxide (Scheme 9). Indeed, Titanium silicates (TS) are tetrahedral Ti(IV) in the network with O and Si. In the presence of H₂O₂, these species could be changed the coordinated number to (VI).⁴³ In this case, they often exist in the dioxirane form and they are able to electrophilic addition to triglycerides and release the epoxidized products.⁴⁴⁻⁴⁵



Scheme 9: Mechanism for epoxidation of triglycerides catalyzed by Titanium silicates

However, the main disadvantage of the microporous titanium silicates is the size of their pores (5.1-5.6 Å) which is a smaller size compared with methyl oleate.⁴⁶ Then, they

⁴¹ M. Janković, S. Sinadinović-Fišer, O. Govedarica, *Ind. Eng. Chem. Res.* **2014**, 53, 9357–9364.

⁴² E. Milchert, K. Malarczyk-Matusiak, M. Musik, *Pol. J. Chem. Technol.* **2016**, 18, 128–133.

⁴³ F. Geobaldo, S. Bordiga, A. Zecchina, E. Giamello, G. Leofanti, G. Petrini, *Catal. Lett.* **1992**, 16, 109–115.

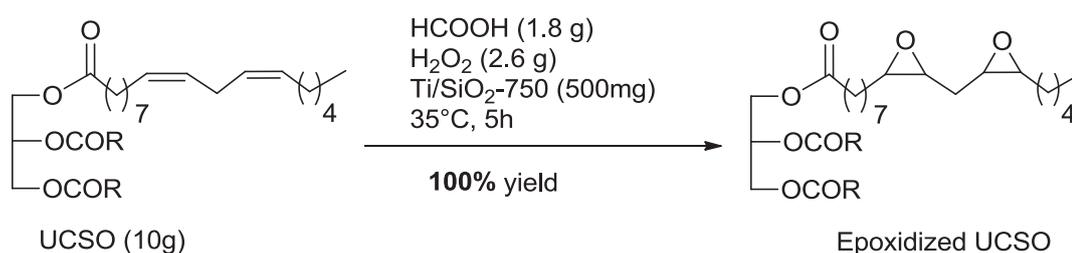
⁴⁴ B. Notary, *Catal. Today* **1993**, 18, 163–172.

⁴⁵ D. R. C. Huybrechts, I. Vasen, H. X. Li, P. A. Jacobs, *Catal. Lett.* **1991**, 8, 237–244.

⁴⁶ S. S. Vieira, Z. M. Magriotis, M. F. Ribeiro, I. Graça, A. Fernandes, J. M. F. M. Lopes, S. M. Coelho, N. A. V. Santos, *Microporous Mesoporous Mater.* **2015**, 201, 160–168.

allowed to access with only a small substrate. However, the epoxidation process occurred only on the external surface of titanium silicates. That is why it is more difficult to epoxidize triglyceride derivatives which have a more bulky structure. To improve this feature, TS was modified in order to obtain high specific-area materials. Indeed, there are two types of mesoporous titanium silicates materials: ordered and disordered. The first type, known from the early 1990's, includes various mesostructure materials such as MCM-41, MCM-48, SBA-15, FSM-16, etc. The second type includes amorphous mixed oxide, which are less studied than the first type.⁴⁷ According to Guidotti *et al.*, the epoxidation of methyl oleate in the presence of Ti-MCM-41 gave an excellent conversion (96%) and selectivity (95%) of epoxidized products. Otherwise, the rate of the introduction of hydrogen peroxide had an influence to control the configuration of the epoxidized products. The epoxidation was performed in a slow addition of H₂O₂ and 85% of cis-epoxide was obtained.⁴⁸ Recently, Yamashita *et al* developed a method to incorporate titanium silicate onto the surface of nanotube architectures. Satisfyingly, the rate of epoxidation of methyl oleate was increased by 3.8 times compared with Ti-containing mesoporous silicates and an excellent selectivity (98%) was achieved. Moreover, only few leaching or deactivation of catalyst were observed, indicating a robust and efficient heterogenous catalytic system.⁴⁹

Ti/SiO₂ was next used as a nanosized solid catalyst for the epoxidation of used cotton seed oils (UCSO).⁵⁰ The reaction was carried out in the presence of hydrogen peroxide and formic acid with a catalytic amount of Ti/SiO₂ at 35°C. After 5 hours, the catalyst was separated through filtration and a quantitative yield of epoxide (100%) was obtained (Scheme 10). Furthermore, this catalyst could be re-used over 5 cycles without loss of any activity. However, the yield of desired products dropped significantly in the 6th and 7th cycles, due to the leaching of Titanium species (0.15%w for each run) during the re-calcination process before reusing the catalyst.



Scheme 10: Epoxidation of used cotton seed oil in the presence of Ti/SiO₂

Finally, the development of economical and ecological epoxidation process would require new heterogenized catalysts which own high leaching-stability, good water-

⁴⁷ O. A. Kholdeeva, N. N. Trukhan, *Russ. Chem. Rev.*, **2006**, 75, 411–432.

⁴⁸ M. Guidotti, E. Gavrilova, A. Galarneau, B. Coq, R. Psaro, N. Ravasio, *Green Chem.* **2011**, 13, 1806–1811.

⁴⁹ T. Kamegawa, D. Yamahana, H. Seto, H. Yamashita, *J. Mater. Chem. A.* **2013**, 1, 891–897.

⁵⁰ D. Kumar, A. Ali, *Energy Fuels* **2012**, 26, 2953–2961.

tolerance such as the combination Niobium- or Titanium-based with POMs and metal-organic frameworks (MOFs) that have high surface area, crystalline-open structure and tunable pore size.^{9,51}

2.1.5 Applications

Epoxidized vegetable oils (EVOs) are the most important platforms in oleochemical industries. They are used not only as intermediates for synthesizing higher value-added compounds such polyols, polyesters or polyurethanes but also own numerous applications. In the past, EVOs were considered as the typical non-metallic stabilizers and secondary plasticizers for the production of PVC materials.⁵²⁻⁵³ Indeed, epoxy group in EVOs could absorb the hydrochloric acid gas (HCl) which is released from PVC during thermal process, thus leading to the increase of the stability of PVC or other halogenated polymers. On the other side, EVOs were also used as plasticizers for Poly Lactic Acid (PLA). A study showed that a blend mixture of PLA and epoxidized sunflower oils could improve the physical properties such as melt rheology and tensile strength.

Furthermore, EVOs were used as potential bio-lubricants.⁵⁴ It should be reminded that EVOs are high molecular weight molecules with high boiling point, non-toxic, cheap and biodegradable. Furthermore, they have good properties required for lubricants such as high viscosity, low volatility. Other application of EVOs is the production of (nano)-composites. Actually, composite materials that were obtained from vinylation of EVOs, exhibited a great viscoelastic properties as natural rubbers. Because of that, composites are used in various construction fields such as roof, floor, wall of houses or some container materials. Moreover, reinforcement of nanocomposites by coating with some metal oxides such as Titanium-(IV) oxide could improve the physical properties and help to broaden the applications. Finally, EVOs were also used for the preparation of paints, coatings, adhesives or phenolic resins.⁵⁵

2.2 Monoketone

Ketone derivatives are important intermediates to functionalize organic molecules and materials. The oxygenation of olefin substrates is the most straightforward and fastest way to access this kind of compound. Indeed, there are many methods related to this transformation. However, only the advanced ones that could be applicable to oleochemical platforms will be presented.

⁵¹ D.-Y. Du, J.-S. Qin, S.-L. Li, Z.-M. Su, Y.-Q. Lan, *Chem. Soc. Rev.* **2014**, *43*, 4615-4632.

⁵² M. T. Taghizadeh, N. Nalbandi, A. Bahadori, *EXPRESS Polym Lett.* **2008**, *2*, 65-76.

⁵³ H. Hosney, B. Nadiem, I. Ashour, I. Mustafa, A. El-Shibiny *J. Appl. Polym. Sci.* **2018**, DOI: 10.1002/APP.46270

⁵⁴ A. Adhvaryu, S.Z. Erhan, *Ind. Crops Prod.* **2002**, *15*, 247-254.

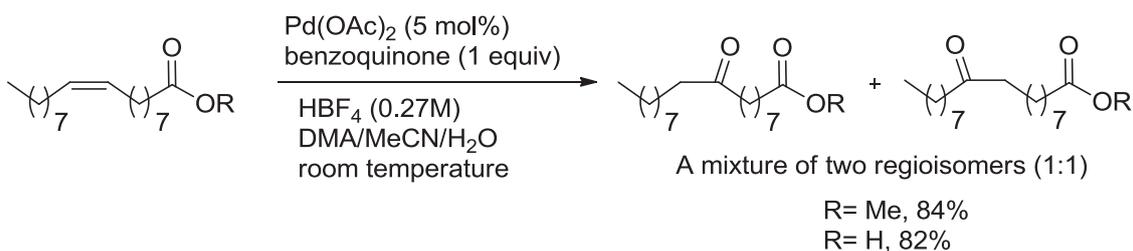
⁵⁵ Nikesh B. Samarth, Prakash A. Mahanwar, *Open J. Org. Polym. Mat.* **2015**, *5*, 1-22.

2.2.1 Wacker-Tsuji oxidation

Wacker-Tsuji oxidation of olefin is the most efficient route to prepare ketone derivatives. Originally, terminal olefins were oxidized to ketones, catalyzed by PdCl₂ in the mixture of solvent H₂O/DMF, then Copper and oxygen were used to re-oxidize the Pd-species and close the catalytic cycle.⁵⁶ One of the most typical examples for application of this oxidation was the production of acetaldehyde from ethylene.¹⁴ However, this method requires of a large amount of CuCl, leading to moderate yields (approximately 70%) and is limited to terminal olefins. With internal olefins, isomerization of C=C bond occurred and low yields of ketones were obtained. Recently, some advances were made to improve the conversion and yield of the desired compound derived from internal substrates as well as to eliminate some drawbacks such the amount of Cu species.

In 2009, Kumada *et al* demonstrated an oxidation of internal olefin using a catalytic amount of PdCl₂ with several advantages such as high conversion and selectivity, copper-free, moderate temperature (80°C) and pressure (3 bar O₂).⁵⁷⁻⁵⁸ However, this method requires a special apparatus (autoclave) and high pressure of oxygen (9 bar O₂ before introducing alkenes followed by charging the autoclave with 3 bar of oxygen).

More recently, Grubbs *et al.* described a catalytic method for the synthesis of ketones from both terminal and internal, alkyl and aromatic olefins.⁵⁹⁻⁶⁰ This process requires a simple palladium complex, a cheap oxidant (benzoquinone or oxygen), and was performed at room temperature. Moreover, this catalytic system could be used in the presence of different functional groups such alcohol, acid, ester, etc, indicating the tolerance of the method. Furthermore, this method was applicable not only to the aromatic substrates but also to oleochemical compounds. For example, the application of this method to methyl oleate gave 84% yield of a 1:1 mixture of two fatty ketone regioisomers (Scheme 11).



Scheme 11: Synthesis of monoketone derived from oleic acid derivatives

⁵⁶ J. Tsuji, *Synthesis* **1984**, 5, 369-384.

⁵⁷ T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem.* **2010**, 122, 1260-1262.

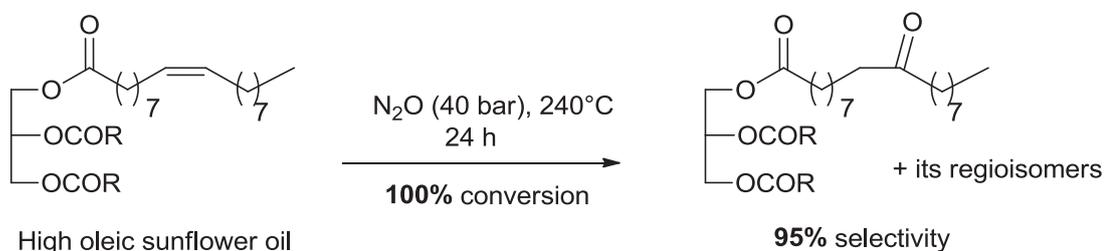
⁵⁸ T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem.* **2006**, 118, 495-499.

⁵⁹ B. Morandi, Z. K. Wickens, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2013**, 52, 2944-2948.

⁶⁰ B. Morandi, Z. K. Wickens, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2013**, 52, 9751-9754.

2.2.2 Nitrous oxidation

Besides the Wacker-Tsuji oxidation, the ketonization of methyl oleate or triglyceride derivatives has gained more attention. Recently, Sels *et al.* disclosed a one-step procedure for solvent- and metal-free oxyfunctionalization of unsaturated fatty methyl esters and vegetable oils using nitrous oxide (N₂O) as an oxidant.⁶¹ The oxidation of methyl oleate was investigated at 220°C in an autoclave that was charged with 40 bar of N₂O. After 8 hours, an excellent conversion of methyl oleate (98%) was obtained and a good selectivity of oxo-compounds (99%) was achieved. A high oleic sunflower oil containing more than 90% of oleic moiety, was also investigated. The same conditions were used for ketonization of HOSO (240°C, 40 bar N₂O) (Scheme 12). A quantitative conversion, with a ketone selectivity over 95%, was achieved within 24 hours, emphasizing the versatility of the method and could be used for valorization of wasted vegetable oils. However, the harsh conditions of the process (high temperature, elevated pressure) could limit its application.



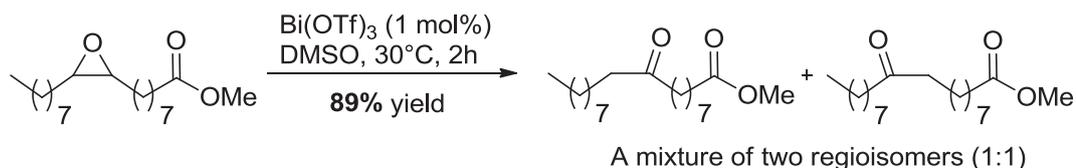
Scheme 12: Ketonization of high-oleic sunflower oil in the presence of nitrous oxide

2.2.3 Meinwald rearrangement

Other possible route to approach ketone compounds is the conversion of epoxidized substrates. In early work, Meinwald reported that epoxidized substrates could be converted to ketones *via* a Meinwald rearrangement in the presence of a Lewis acid.²⁰ Several studies were done on aromatic derivatives but there are a few studies on oleochemical platforms. Generally, ketone compounds were considered as un-wanted products from epoxidation process. In 2013, Doll *et al.* reported a simple method to synthesize ketones from epoxidized methyl oleate (Scheme 13).⁶² The reaction was investigated in the presence of Bi(OTf)₃ (1 mol%) at 30°C using DMSO as a solvent and a sole oxidant. A good yield (89%) of ketone derivatives was isolated after 2 hours. However, this method suffers from the non-recyclable metal catalyst and the used of a high boiling point solvent such as DMSO.

⁶¹ I. Hermans, K. Janssen, B. Moens, A. Philippaerts, B. Van Berlo, J. Peeters, P. A. Jacobs, B. F. Sels, *Adv. Synth. Catal.* **2007**, *349*, 1604-1608.

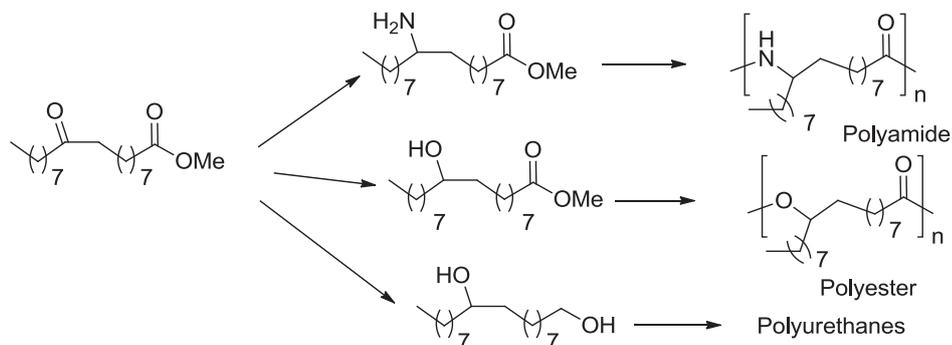
⁶² K. M. Doll, G. B. Bantchev, R. E. Murray, *ACS Sustainable Chem. Eng.* **2013**, *1*, 39-45.



Scheme 13: Preparation of fatty ketone from epoxidized methyl oleate catalyzed by $\text{Bi}(\text{OTf})_3$

2.2.4 Applications: polyesters, polyamides

Ketones are important intermediates in organic synthesis. For example, they could be converted to hydroxy or amino group (Scheme 14). These compounds could be polymerized to provide new bio-based (co)polymers which could improve the physical properties of the original polymer. For instance, the amino-ester could be synthesized *via* reductive amination of ketone derived from methyl oleate, and could be used as co-polymer with nylon-6,6 to significantly reduce its water-uptake.⁶³ Moreover, ketones derived from soybean oil were directly used for the formulation of lubricants and bio-based dielectric fluids.⁶⁴



Scheme 14: Potential polymers derived from vegetable oil ketone derivatives

2.3 Cyclic carbonates

Nowadays, the preparation of cyclic carbonates has received more and more interests due to their applications. First of all, some small carbonates such ethylene carbonate, propylene carbonate are used as polar, high boiling point solvents in organic synthesis as well as electrolytes in the production of Lithium batteries. Secondly, cyclic carbonates are also starting materials for the production of polycarbonates and polyurethanes (PUs) that are used as thermoplastic, foaming, coating and adhesive materials.⁶⁵ Indeed, the world's production of polyurethane reached 20.4 million tons in 2017,⁶⁶ in which most of them were prepared *via* the conventional pathway: condensation of polyol and isocyanate substrates that are highly toxic. Then, the alternative generation of PUs, known as non-isocyanate polyurethanes (NIPUs), is the condensation of cyclic carbonates and polyamines. Actually, there are two main routes to

⁶³ M. Winkler, M. A. R. Meier, *Green Chem.* **2014**, *16*, 1784–1788.

⁶⁴ N. W. Higgins, J. F. Stults, *U.S. Patent 7947847*, May 24, 2011.

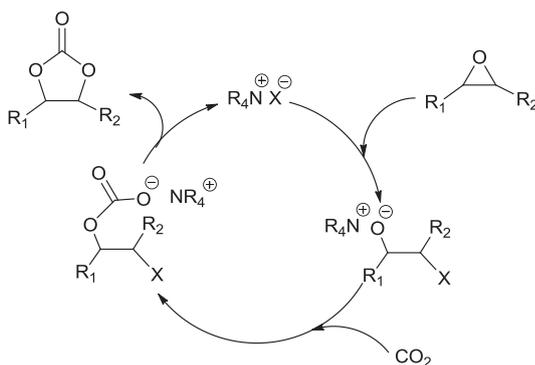
⁶⁵ D. C. Webster, *Prog. Org. Coat.* **2003**, *47*, 77–86.

⁶⁶ <https://www.statista.com/statistics/720341/global-polyurethane-market-size-forecast/>, Retrieved in May 21st 2018.

synthesize these intermediates. The first pathway involves the condensation of diol with dialkyl carbonate or phosgene. However, this method suffers from the formation of alcohol or hydrochloride as co-products or using an extremely toxic agent (COCl_2). The second route is the fixation of CO_2 and epoxidized substrates. This method provides a 100% atom economy and valorizes carbon dioxide which is a global warming agent. It is possible to couple CO_2 with epoxidized vegetable oils (EVOs) to synthesize carbonated vegetable oils (CVOs) then to prepare new types of bio-based polyurethanes. There are a great number of catalytic systems for the addition of carbon dioxide into epoxide substrates but only efficient methods that were applied to oleochemical platforms will be presented.

2.3.1 Quaternary ammonium salts

Quaternary ammonium halides were first used as catalysts for fixation of CO_2 onto epoxidized substrates. Basically, in the presence of ammonium salt, the oxirane could be activated, thus the halides could attack the epoxide to open this compound, following by the addition of CO_2 and epoxide ring-closing to release the cyclic carbonate and halide anion (Scheme 15).⁶⁷

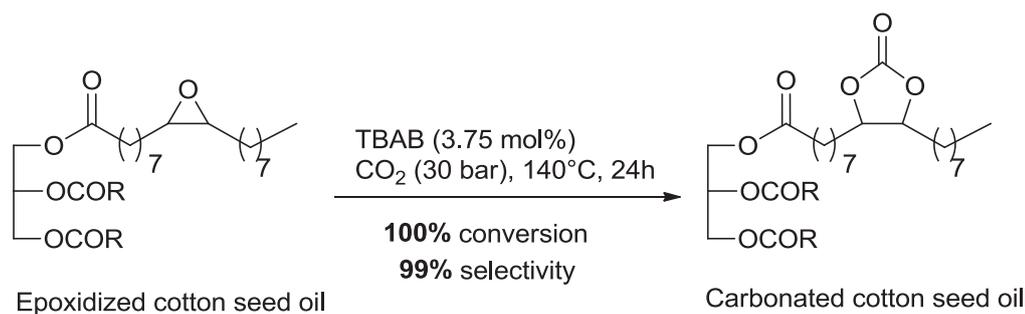


Scheme 15: Mechanism of the fixation of CO_2 into cyclic carbonates catalysed by tetraalkyl ammonium halides

There are many types of tetraalkyl ammonium halides used for this transformation and they exhibit different activities, depending on the counter-anion. On the one hand, TBAC and TBAF gave poor results with the coupling of CO_2 and epoxides. On the contrary, TBAB and TBAI provided good results even with the non-polar, unactivated oxirane substrates such as EVOs. According to Hou *et al.*, carbonation of epoxidized cotton seed oil was investigated in the presence of TBAB (3.75 mol%) at 140°C in compressed CO_2 (30 bar) (Scheme 16).⁶⁸ A quantitative conversion of ECSO was observed with an excellent selectivity (99%) of desired product after 24 hours. Moreover, the carbonated oil was used as new bio-lubricants. However, this catalyst could not be reused.

⁶⁷ M. Alves, B. Grignard, R. Mereau, C. Jerome, T. Tassaing, C. Detrembleur, *Catal. Sci. Technol.* **2017**, *7*, 2651–2684.

⁶⁸ L. Zhang, Y. Luo, Z. Hou, Z. He, W. Eli, *J. Am. Oil Chem. Soc.* **2014**, *91*, 143–150.



Scheme 16: Preparation of carbonated cotton seed oil in the presence of TBAB

To recycle these catalysts, immobilization of quaternary ammonium on solid carriers such as polymer,⁶⁹ silica⁷⁰ has been performed. There have been a few methods to immobilize the active species on supported materials. On the one hand, the trialkylamine could be grafted on halide-functionalized polymers. On the other hand, ammonium salts could be immobilized onto surface of materials by physisorption. Most of these catalysts exhibit high conversion and selectivity and could be re-used but some drawbacks remain such as harsh conditions (elevated pressure (20-80 bar) of CO₂) and limited conversion for disubstituted substrates and EVOs.

2.3.2 Phosphonium salts

Phosphonium salts could also be used as catalysts for coupling CO₂ and epoxides. An initial attempt was reported by Nishikubo *et al.*, employing tetrabutyl phosphonium bromide as a catalytic active species. A moderate yield (35%) was obtained for phenoxy methyl epoxide, similarly than ammonium salt.⁷¹ However, the use of phosphonium salts for this reaction was quite underexploited. Recently, Werner *et al.* reported a catalytic system consisting of MoO₃ and [Bu₄P]Br.⁷² In the presence of MoO₃ as an activating agent of epoxide and phosphonium bromide as a nucleophilic catalyst at 100°C and 50 bar of CO₂, the carbonation of epoxidized high-oleic sunflower oil provided a good conversion (99%) and selectivity (95%) after 20 hours (Scheme 17). A similar work was also reported Büttner *et al.*, replacing the Mo-based catalyst by an iron-based catalyst such as FeCl₃.⁷³ Similar performances were obtained with epoxidized FAMES or EVOs.

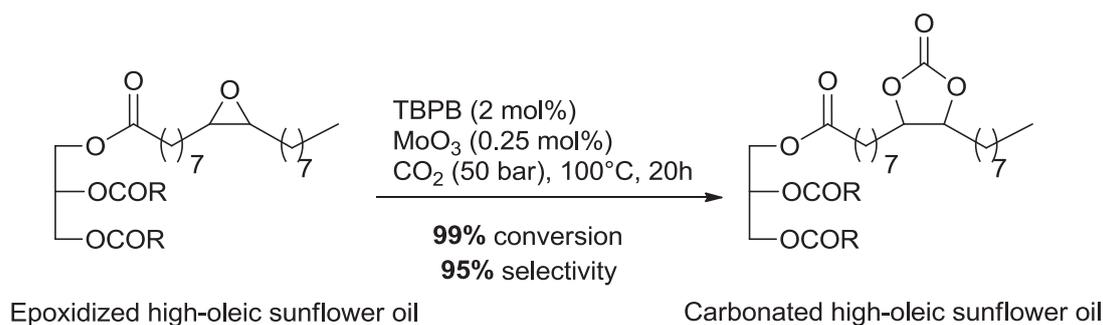
⁶⁹ X. Chen, J. Sun, J. Wang, W. Cheng, *Tetrahedron Lett.* **2012**, *53*, 2684-2688.

⁷⁰ J.-Q. Wang, D.-L. Kong, J.-Y. Chen, F. Cai, L.-N. He, *J. Mol. Catal. A* **2006**, *249*, 143-148.

⁷¹ T. Nishikubo, A. Kameyama, J. Yamashita, M. Tomoi, W. Fukuda, *J. Polym. Sci. Part A* **1993**, *31*, 939-947.

⁷² N. Tenhumberg, H. Büttner, B. Schäffner, D. Kruse, M. Blumensteinc, T. Werner, *Green Chem.* **2016**, *18*, 3775-3788.

⁷³ H. Büttner, C. Grimmer, J. Steinbauer, T. Werner, *ACS Sustainable Chem. Eng.* **2016**, *4*, 4805-4814.



Scheme 17: Catalytic carbonation of epoxidized high-oleic sunflower oil in the presence of Mo-based catalyst and tetrabutyl phosphonium bromide

To improve the efficiency and the recycling capacity of these catalysts, some heterogeneous versions of phosphonium salts were developed, in which tetrabutyl phosphonium halide was grafted on fluorinated polymer⁷⁴ or silica.⁷⁵⁻⁷⁶ Sakakura *et al.* were the first to report the immobilization of phosphonium halide onto silica.⁷⁵ In this case, silanol group (Si-OH) in silica could play the role of an activating agent for the epoxide and halide as nucleophilic agent, leading to a synergistic effect on the fixation of carbon dioxide onto epoxides. Moreover, this supported catalyst could be easily separated and re-used at least 10 cycles without losing any activity.⁷⁶

Other phosphorous species such as modified cyclotriphosphazane,⁷⁷ azo-phosphatane⁷⁸ or phosphorus ylide⁷⁹ were also considered as catalysts for addition of CO₂ into epoxides. However, most catalysts provided a good yield for terminal epoxides and a limitation of yield of cyclic carbonates were reported for difficult substrates such as disubstituted epoxides or EVOs.

2.3.3 Imidazolium salts

Imidazolium salts are important catalysts for the fixation of CO₂ into epoxidized substrates. However, the use of this family for epoxy fatty platforms is quite underdeveloped. In the literature, there are a few examples for this catalytic transformation. One of them is a carbonation of diepoxy methyl linoleate at 100°C and high pressure of CO₂, using a BMIm-Cl (5 mol%) as the catalyst.⁸⁰ After 17 hours, an excellent selectivity (100%) was observed for the desired product, but the conversion was limited to 26%, due to the bulky structure of internal

⁷⁴ Q.-W. Song, L.-N. He, J.-Q. Wang, H. Yasuda, T. Sakakura, *Green Chem.* **2013**, *15*, 110-115.

⁷⁵ T. Takahashi, T. Watahiki, S. Kitazume, H. Yasuda, T. Sakakura, *Chem. Commun.* **2006**, *15*, 1664-1666.

⁷⁶ T. Sakai, Y. Tsutsumi, T. Ema, *Green Chem.* **2008**, *10*, 337-341.

⁷⁷ P. K. Khatri, S. L. Jain, K. T. Lim, *Tetrahedron Lett.* **2013**, *54*, 6648-6650.

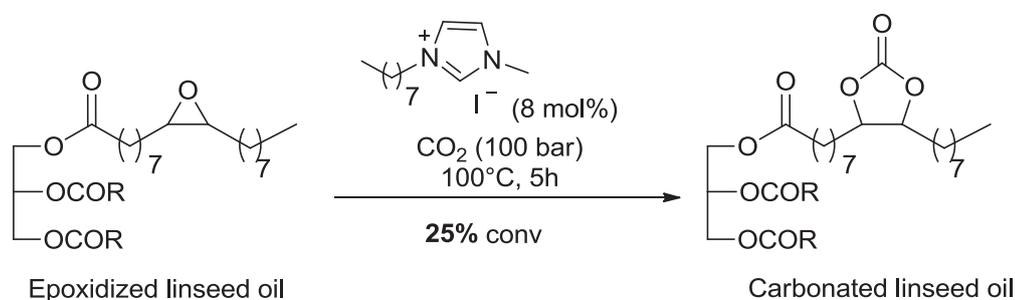
⁷⁸ B. Chatelet, L. Joucla, J.-P. Dutasta, A. Martinez, K. C. Szeto, V. Dufaud, *J. Am. Chem. Soc.* **2013**, *135*, 5348-5351.

⁷⁹ H. Zhou, G.-X. Wang, W.-Z. Zhang, X.-B. Lu, *ACS Catal.* **2015**, *5*, 6773-6779.

⁸⁰ B. Schffner, M. Blug, D. Kruse, M. Polyakov, A. Kçckritz, A. Martin, P. Rajagopalan, U. Bentrup, A. Brckner, S. Jung, D. Agar, B. Rngeler, A. Pfennig, K. Mller, W. Arlt, B. Woldt, M. Graß, S. Buchholz, *ChemSusChem* **2014**, *7*, 1133-1139.

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epoxides. However, the use of imidazolium for the fixation of CO₂ onto terminal and aromatic epoxides was proved a long time ago. Another investigation of the cycloaddition of CO₂ onto epoxidized linseed oil was reported by Tassaing *et al.*⁸¹ Using *n*-octylimidazolium iodide as the catalyst, the carbonation of ELO at 100°C and 100 bar CO₂ provided only 25% conversion after 5 hours (Scheme 18).



Scheme 18: Carbonation of epoxidized linseed oil catalyzed by imidazolium iodide

In 2001, Deng *et al.* were the first to use an imidazolium salt as the active catalyst for the preparation of propylene carbonate.⁸² The reaction was performed at 110°C and 20 bar of CO₂ and gave an excellent conversion and selectivity of carbonate products. The studies also mentioned that the reactivity of imidazolium salts was depending on the length of the alkyl chain and the nature of counter-anion. On the one hand, the increasing of the length of the alkyl chain (C2 to C8) improved the conversion of the cycloaddition.⁸³ On the other hand, iodide and BF₄ anions were the best candidates for fixation of CO₂ due to their strong nucleophilic and good leaving-group abilities.⁸⁴⁻⁸⁵ However, these catalytic systems needed a high temperature and high pressure of CO₂. To improve this feature, a ternary catalyst ZnBr₂/K₂CO₃/ionic liquid was developed by Shi *et al.*, thus allowing the fixation of CO₂ in styrene oxide at room temperature and atmospheric CO₂ (or even with flue CO₂).⁸⁶ In this case, zinc bromide was acting as a Lewis acid to activate the oxirane then imidazolylene-CO₂ adduct was acting as an active species for the formation of a cyclic carbonate. Moreover, this catalytic system could be recycled at least 5 times without significant loss of activity.

Recently, the grafting of imidazolium salt onto supported material has received more attention. The imidazolium species could be immobilized on the surface of fibrous silica,⁸⁷ graphene oxide,⁸⁸ chitosan⁸⁹ or cellulose.⁹⁰ The fixation of CO₂ using these catalysts gave good

⁸¹ M. Alves, B. Grignard, S. Gennen, C. Detrembleur, C. Jerome, T. Tassaing, *RSC Adv.* **2015**, *5*, 53629-53636.

⁸² J. Peng, Y. Deng, *New J. Chem.* **2001**, *25*, 639-641.

⁸³ H. Kawanami, A. Sasaki, K. Matsuia, Y. Ikushima, *Chem. Commun.* **2003**, *0*, 896-897.

⁸⁴ P. Jaiswal, M. N. Varma, *J. CO₂ Util.* **2016**, *14*, 93-97.

⁸⁵ A.-L. Girard, N. Simon, M. Zanatta, S. Marmitt, P. Gonçalves, J. Dupont, *Green Chem.* **2014**, *16*, 2815-2825.

⁸⁶ H. Zhanga, X. Konga, C. Caoa, G. Pangb, Y. Shi, *J. CO₂ Util.* **2016**, *14*, 76-82.

⁸⁷ W. L. Dai, L. Chen, S. F. Yin, S. L. Luo, C. T. Au, *Catal. Lett.* **2010**, *135*, 295-304.

⁸⁸ W. H. Zhang, P. P. He, S. Wu, J. Xu, Y. Li, G. Zhang, X. Y. Wei, *Appl. Catal. A* **2016**, *509*, 111-117.

⁸⁹ J. Sun, J. Wang, W. Cheng, J. Zhang, X. Li, S. Zhang, Y. She, *Green Chem.* **2012**, *14*, 654-660.

⁹⁰ K. R. Roshan, G. Mathai, J. Kim, J. Tharun, G.-A. Park, D.-W. Park, *Green Chem.* **2012**, *14*, 2933-2940.

results for terminal epoxides and the recycling of the catalysts was quite simple. Only best catalytic systems are detailed here such as imidazolium/urea on silica and polyimidazolium on metal-organic frameworks (MOFs). Firstly, the imidazolium-urea network supported on mesoporous silica was reported by Arai *et al.*⁹¹ In this case, there was a double activation of epoxide by urea moiety and proton of the imidazolium salt. The fixation of CO₂ onto propylene oxide was performed at elevated temperature (110°C) and pressure (25 bar CO₂) to give 96% yield after 4 hours. However, the scope was limited for disubstituted oxirane compounds. The synthesis of polyimidazolium was quite interesting feature in the view of capturing CO₂. Vinyl imidazolium halide was self-polymerized, followed by absorption on the surface of high surface materials such as MIL-101.⁹²⁻⁹³ Owing to the high surface area, hierarchical pores and the synergistic effect between the Lewis acid and Lewis base active site, the fixation of carbon dioxide onto oxirane substrates could be performed at moderate temperature (45-70°C) and atmospheric CO₂ and provided good yields of cyclic carbonates. Furthermore, the heterogeneous catalyst could be reused 10 times without losing any activity, highlighting the high efficiency of this catalyst.

2.3.4 Metal-based catalyst

At the very beginning, metal-based catalysts such as ZnBr₂, Zn(OAc)₂ were used as the Lewis acids for the coupling of epoxides and CO₂.⁹⁴ Due to synergistic effects between metal and imidazolium salt, aromatic epoxides could be converted to the corresponding carbonates with a high conversion and selectivity. However, this process was performed at elevated pressure of CO₂ (40 bar) and no example for aliphatic or bulky epoxides was reported.

Recently, there has been a series of publications mentioning that the addition of CO₂ into epoxide could be carried out under milder conditions in the presence of metal complexes. In 2018, Werner *et al.* developed a catalytic system using CaI₂ and 18-crown-6 (5 mol%) in the presence of a cocatalyst such as Ph₃P (5 mol%) for the preparation of carbonated sunflower oil.⁹⁵ The reaction was performed in mild condition (45°C, 5 bar of CO₂). After 24 hours, a quantitative conversion and selectivity were achieved, indicating a powerful catalyst for synthesis of carbonated vegetable oils (Scheme 19).

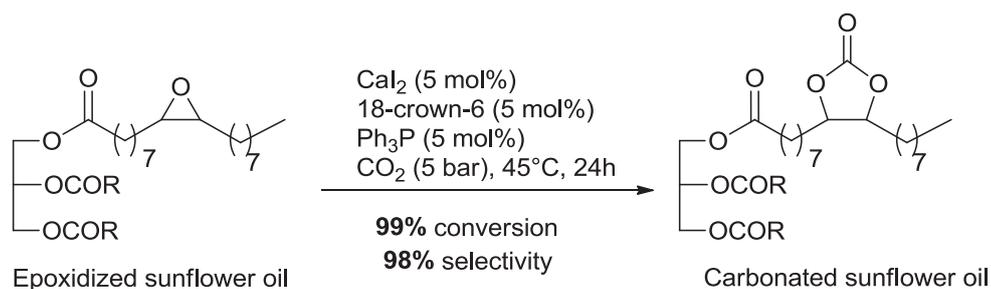
⁹¹ M. Liu, X. Lu, Y. Jiang, J. Sun, M. Arai, *ChemCatChem* **2018**, *10*, 1860-1868.

⁹² Z. Guo, Q. Jiang, Y. Shi, J. Li, X. Yang, W. Hou, Y. Zhou, J. Wang, *ACS Catal.* **2017**, *7*, 6770-6780.

⁹³ M. Ding and H.-L. Jiang, *ACS Catal.* **2018**, *8*, 3194-3201.

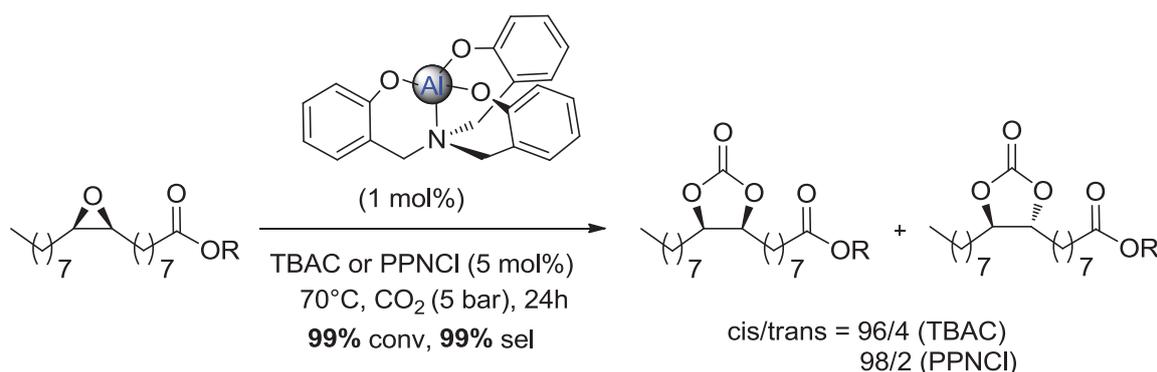
⁹⁴ J. Sun, S. Fujita, F. Zhao, M. Arai, *Green Chem.* **2004**, *6*, 613-616.

⁹⁵ L. Longwitz, J. Steinbauer, A. Spannenberg, T. Werner, *ACS Catal.* **2018**, *8*, 665-672.



Scheme 19: Carbonation of epoxidized sunflower oil in the presence of CaI_2 and 18-crown-6

Kleij *et al.* have also reported on the use of aluminum(III) aminotriphenolate in combination with tetrabutyl ammonium halides or bis(triphenylphosphine)iminium chloride (PPNCl) as the nucleophilic agent for the cycloaddition of CO_2 onto fatty epoxides.⁹⁶ The reaction was investigated at 70°C with 5 bar of CO_2 . After 24 hours, excellent conversion and selectivity (>99%) were observed (Scheme 20). Moreover, this study also mentioned that the stereoselectivity of cyclic carbonates was depending on the nature of the counter-anion. The use of chlorine-based nucleophiles can selectively promote for the formation of *cis*-cyclic carbonates.



Scheme 20: Fixation of CO_2 onto fatty epoxide catalyzed by Al-complex

Porphyrin-based catalysts were also developed for cyclic addition of CO_2 into carbonates by Ema *et al.*^{97,98,99} The catalyst was synthesized by the combination of porphyrin and zinc or magnesium compounds. Later, the tetraalkyl ammonium halide was grafted on the chain of the porphyrin complex to make a binary functionalization of the catalyst. Then, the fixation of carbon dioxide onto epoxides was carried out at 120°C in the presence of CO_2 pressure (17 bar) for 3 hours and provided a good yield for carbonate products. Moreover, this method used a very low catalyst loading with a really high TON (the best performance gave a TON of 240,000). However, the studies focused on terminal epoxides and no example

⁹⁶ L. P. Carrodegas, À. Cristòfol, J. M. Fraile, J. A. Mayoral, V. Dorado, C. I. Herrerías, A. W. Kleij, *Green Chem.* **2017**, *19*, 3535–3541.

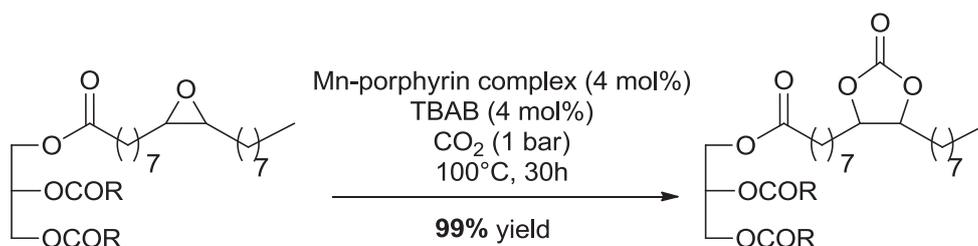
⁹⁷ T. Ema, Y. Miyazaki, J. Shimonishi, C. Maeda, J. Hasegawa, *J. Am. Chem. Soc.* **2014**, *136*, 15270–15279.

⁹⁸ C. Maeda, T. Taniguchi, K. Ogawa, T. Ema, *Angew. Chem. Int. Ed.* **2015**, *54*, 134–138.

⁹⁹ C. Maeda, J. Shimonishi, R. Miyazaki, J. Hasegawa, T. Ema, *Chem. Eur. J.* **2016**, *22*, 6556–6563.

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with fatty substrates was reported. More recently, simple conditions for carbonate vegetable oils were developed by Safari *et al.*, based on a binary complex of Mn-porphyrin and tetrabutylammonium bromine.¹⁰⁰ In the presence of 4 mol% of catalytic system, the coupling of CO₂ and epoxidized sunflower oil gave an excellent yield (99%) after 30 hours under atmospheric CO₂ (Scheme 21). Moreover, this catalyst could be recycled several times. However, the yield significantly dropped from 99% in the 1st run to 62% in the 5th run, maybe due to the leaching of Mn-complex, highlighting the limitation of this process.



Scheme 21: Carbonation of epoxidized sunflower oil in the presence of Mn-porphyrin and TBAB

2.4 Diols

Among all derivatives of vegetable oils, vicinal diols (or dihydroxylated fatty compounds) are also interesting platforms with a wide range of applications. First of all, oleochemical diols were used in the conventional production of polyurethanes *via* condensations of polyols and polyisocyanates.¹⁰¹ This family of polymers displays a good behavior in thermoplastics, elastomers, etc. There are various applications using polyurethanes in the production of elastomers, foaming and coating materials. Secondly, diol derivatives could be used as intermediates in the production of estolides or hyperbranched polyesters.¹⁰² Furthermore, diacyl originated from diol substrates could be used as alternative bio-lubricants.¹⁰³⁻¹⁰⁴ On the other side, dihydroxylated fatty compounds are important intermediates in the oleochemical transformations. They could be cleaved in the presence of metal (Ru, Mo, W, etc) with an oxidant (oxygen, hydrogen peroxide and oxone) to pelargonic and azelaic acids that have a large market in pesticides, plasticizers or in the polymer industry.¹⁰⁵ Moreover, this type of intermediates could be also cleaved into two aldehydes: nonanal and methyl azelaaldehyde which are used in

¹⁰⁰ A. Farhadian, M. B. G. Afshani, A. B. Miyardan, M. R. Nabid, N. Safari, *ChemistrySelect* **2017**, *2*, 1431 – 1435.

¹⁰¹ H.-W. Engels, H.-G. Pirkel, R. Albers, R. W. Albach, J. Krause, A. Hoffmann, H. Casselmann, J. Dormish, *Angew. Chem. Int. Ed.* **2013**, *52*, 9422 – 9441.

¹⁰² B. Testud, D. Pintori, E. Grau, D. Taton, H. Cramail, *Green Chem.*, **2017**, *19*, 259–269.

¹⁰³ A. Sammaiah, K. V. Padmaja, R. B. N. Prasad, *J. Agric. Food. Chem.* **2014**, *62*, 4652-4660.

¹⁰⁴ W. Riemenschneider, *Ullmann's Encyclopedia of Industrial Chemistry*, Carboxylic Acids, Aliphatic, **2010**, DOI: 10.1002/14356007.a05_235.

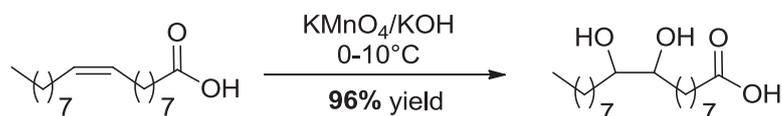
¹⁰⁵ B. Cornils, P. Lappe, *Ullmann's Encyclopedia of Industrial Chemistry*, Dicarboxylic Acids, Aliphatic, **2010**, DOI: 10.1002/14356007.a08_523.pub2.

the production of perfumes, bio-surfactants or polymers.¹⁰⁶ Some of the preparation of polyols derived from vegetable oil derivatives are presented below.

2.4.1 Dihydroxylation

2.4.1.1 KMnO_4

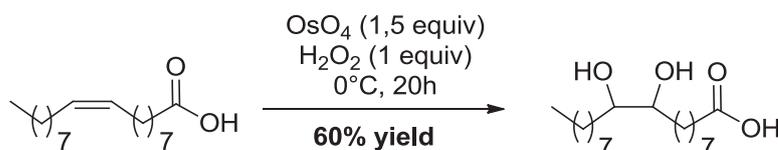
In a very early report (1925), a dilute alkaline solution of KMnO_4 was used for the dihydroxylation of oleic acid. Reported by Lapworth *et al.*,¹⁰⁷ the conditions for this process should be carefully controlled: 1) the temperature should be controlled between 0-10°C, 2) the concentration of oleic acid (to make the salt) should not exceed 1%, 3) the concentration of KMnO_4 should not exceed 1%, 4) a short-period of reaction time (5 minutes) and a slight excess of alkaline solution (KOH or NaOH) was necessary to avoid the generation of α -hydroxyketone fatty derivatives. Following such precise conditions, an excellent yield of 9,10-dihydroxy octadecanoic acid (96% yield) was achieved (Scheme 22).



Scheme 22: Dihydroxylation of fatty acid in the presence of an alkaline solution of KMnO_4

2.4.1.2 Upjohn dihydroxylation

The direct dihydroxylation of oleic acid was reported by Milas *et al.*, using a stoichiometric amount of OsO_4 as an oxidant and hydrogen peroxide as a co-oxidant (for re-oxidation of Os(VI) to Os(VIII)).¹⁰⁸ The reaction was carried out at 0°C for 20 hours and provided a moderate yield of the corresponding diol (60%) (Scheme 23). However, OsO_4 is extremely toxic and expensive. Therefore, its use should be limited in the catalytic amount.



Scheme 23: Dihydroxylation of fatty substrate in the presence of stoichiometric of OsO_4

Recently, several advances were reported to avoid the limitations of Milas's methods. A catalytic amount of OsO_4 was used instead of an excess amount. An excess of *N*-methylmorpholine was used in order to re-oxidize the Os(VI) to Os(VIII) species.¹⁰⁹ Furthermore, another peroxide such as *t*-butyl hydroxyperoxide (TBHP) could be used as a

¹⁰⁶ C. Kohlpaintner, M. Schulte, J. Falbe, P. Lappe, J. Weber, G. D. Frey, *Ullmann's Encyclopedia of Industrial Chemistry*, Aldehyde aliphatic, **2013**, DOI: 10.1002/14356007.a01_321.pub3.

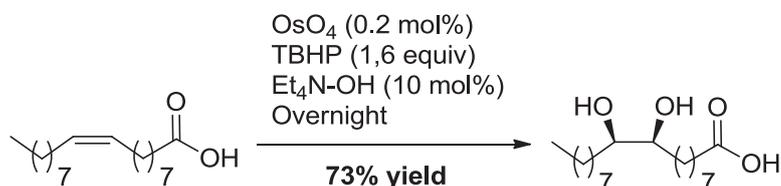
¹⁰⁷ A. Lapworth, E. N. Motteam, *J. Chem. Soc., Trans.* **1925**, 127, 1628-1631.

¹⁰⁸ N. A. Milas, S. Sussman, H. S. Mason, *J. Am. Chem. Soc.* **1939**, 61, 1844-1847.

¹⁰⁹ H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, 94, 2483-2547.

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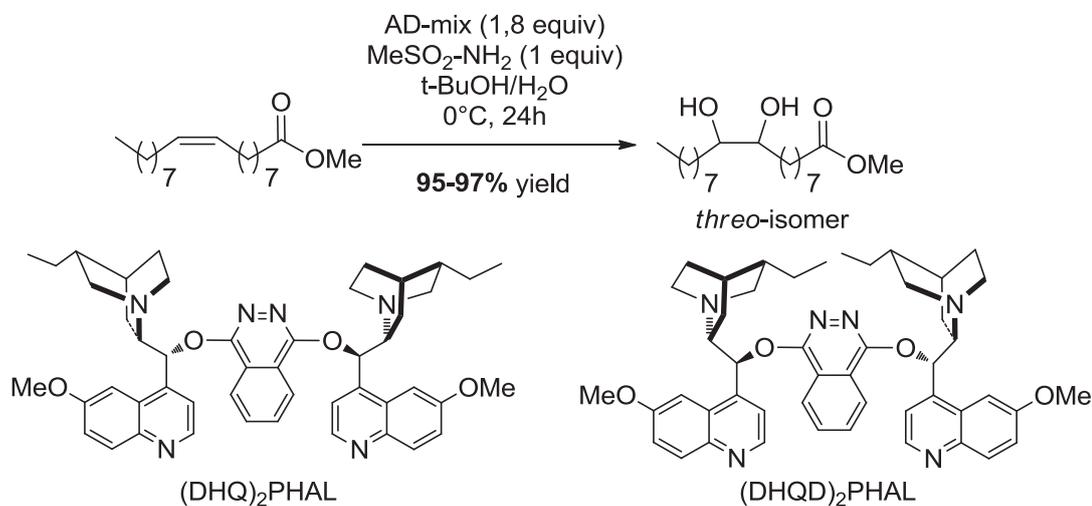
co-oxidant that enables the use of a small amount of osmium catalyst. According to Sharpless and Akashi, the dihydroxylation of oleic acid provided a moderate yield (73%) of *cis*-diol with the catalytic system OsO₄/TBHP in basic media (Scheme 24).¹¹⁰



Scheme 24: Dihydroxylation of oleic acid in the presence of the catalytic system OsO₄/TBHP

2.4.1.3 Sharpless dihydroxylation

In order to access a highly-pure enantiomer of vicinal fatty diols, Sharpless *et al.* developed a new process, using osmium as a catalyst and a stoichiometric amount of NMO or K₃Fe(CN)₆ as the co-oxidant. Moreover, to control the enantioselectivity, the reaction required the use AD-mix- α or AD-mix- β . The enantioselectivity of the desired product was achieved *via* the addition of chiral quinine ligand into osmium-based catalyst, leading to control the side of the attack. In 1997, Schäfer *et al.* applied this strategy to fatty substrates (Scheme 25).¹¹¹ For example, the sharpless dihydroxylation of methyl oleate provided a good isolated yield of *threo*-isomers (97-95%) with high enantiomeric excess (95-97%).



Scheme 25: Sharpless dihydroxylation of methyl oleate

2.4.1.4 Prévost-Woodward dihydroxylation

In order to replace the use of highly toxic metal such as osmium, Prévost proposed to carry out the dihydroxylation of olefin using silver benzoate and iodide in alkaline solution.¹¹²

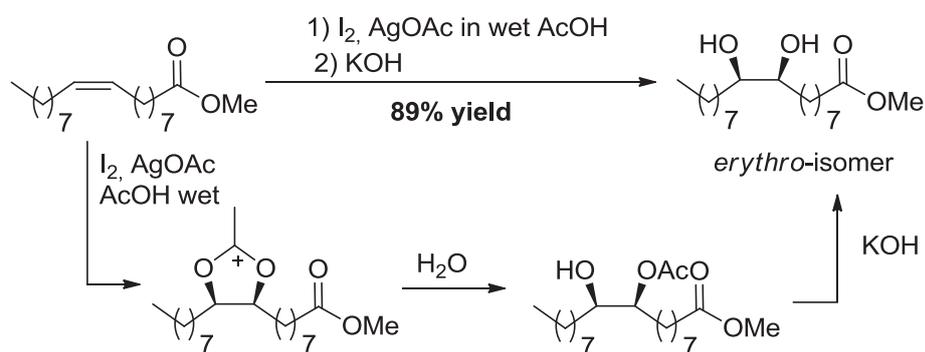
¹¹⁰ K. B. Sharpless, K. Akashi, *J. Am. Chem. Soc.* **1976**, *98*, 1986-1987.

¹¹¹ M. Plate, M. Overs, H. J. Schäfer, *Synthesis* **1998**, *9*, 1255-1258.

¹¹² C. Prévost, *Comptes Rendus* **1933**, *196*, 1129-1131.

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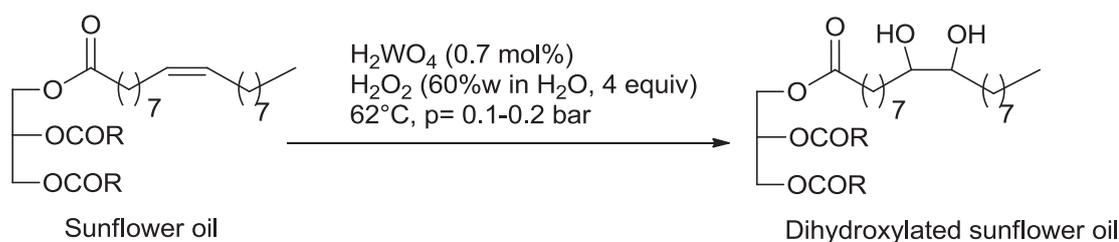
First of all, the formation of a cyclic iodonium was performed in the presence of iodine, followed by nucleophilic substitution of benzoate anion to generate a *anti*-disubstituted dibenzoate intermediate. Finally, this species was hydrolyzed in the alkaline solution to give the *anti*-diol. Later, Woodward developed a modification to synthesize *syn*-diol.¹¹³ The key of this process is the nucleophilic substitution of cycloiodonium in wet acetic acid. Considering the acetate was less hindered than the benzoate and contains an amount of water, the cyclic intermediate was cleaved into *syn*-monoacylated diol. Finally, the hydrolysis was performed in alkaline condition to give a good yield of *syn*-diol. In 1957, Gunstone and Morris have applied the Woodward modification to fatty substrates including triglycerides.¹¹⁴ The process worked well for methyl oleate and gave a good yield (89%) of *erythro*-diol (Scheme 26).



Scheme 26: Woodward dihydroxylation of methyl oleate

2.4.1.5 NOVAMONT process

In 2010, NOVAMONT Corporation developed a one-step process to prepare dihydroxylated vegetable oils in continuous flow.¹¹⁵ The process was based on domino reactions: epoxidation and hydrolysis, catalyzed by a mineral acid, in which the best performance was given by tungstic acid (H₂WO₄). Hydrogen peroxide was used as an oxidant and the process was performed at 62°C under reduced pressure. Moreover, it should be noted that the addition of hydrogen peroxide is a highly exothermic process. Consequently, the amount of hydrogen peroxide should be introduced dropwise in flow. When the addition of the oxidizing agent was complete, the reaction was extended for 2-4 hours and gave a good yield of hydroxylated triglycerides (Scheme 27).



¹¹³ R. B. Woodward and F. V. Brutcher Jr., *J. Am. Chem. Soc.* **1958**, *80*, 209-211.

¹¹⁴ F. D. Gunstone and L. J. Morris, *J. Chem. Soc.* **1957**, *0*, 487-490.

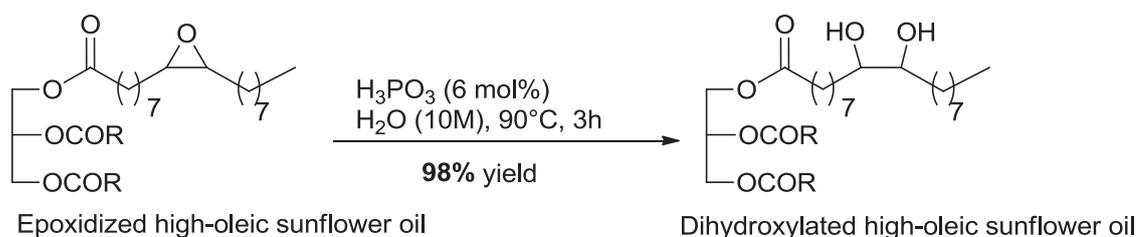
¹¹⁵ A. Bieser, G. Borsotti, F. Digioia, A. Ferrari, A. Pirocco, WO2011080296A1.

Scheme 27: Dihydroxylation of sunflower oil catalyzed by H_2WO_4 in continuous flow

2.4.2 Oxiranes ring-opening

2.4.2.1 Acid-catalyzed

To simplify the procedure for the preparation of vicinal diols and to avoid the formation of by-products from the one-step synthesis, some researchers studied the ring-opening of epoxidized fatty derivatives in the presence of acid catalyst. According to Blach *et al*, the epoxidized vegetable oil was prepared *via* a traditional epoxidation pathway, using a mixture of formic acid and hydrogen peroxide at 60°C for 4 hours.¹¹⁶ Then, the hydrolysis of epoxides was studied at 90°C using a catalytic amount of a series of acid such as HCl, H_2SO_4 , H_3PO_4 , etc. These studies also indicated that a good yield (> 80%) of dihydroxylated substrates were obtained in the presence of a strong mineral acid. A specific effect was observed when using phosphorous acid (H_3PO_3) as a catalyst, exhibiting an excellent yield of desired products (98%) (Scheme 28).

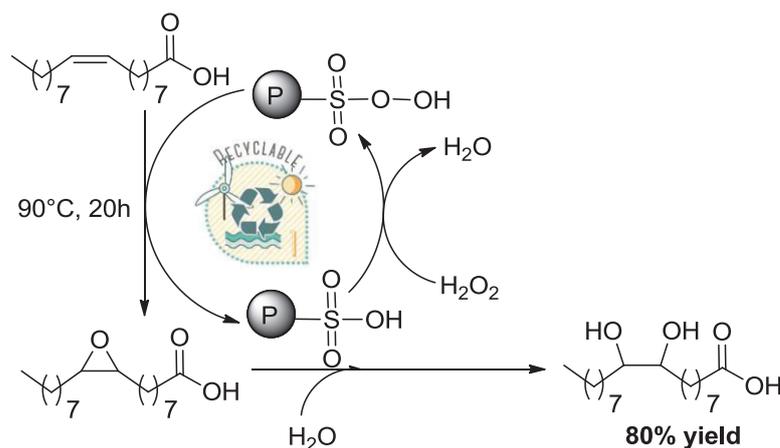


Scheme 28: Ring-opening of epoxidized sunflower oil in the presence of acid catalyst

Even if this process is a simple procedure and uses a catalytic amount of mineral acid, this catalyst could not be reused. In the view of green chemistry, especially the use of recyclable catalysts, Sato *et al.* proposed a procedure for the synthetic of vicinal biosourced diol in the presence of a catalytic amount of an acid resin such as Nafion-50.¹¹⁷ Starting from oleic acid, the hydroxylation process occurred in 2 steps through the epoxidation (acid catalyzed, H_2O_2), following by ring-opening of oxiranes (acid catalyzed, H_2O) to give a good yield of diol product (80%) (Scheme 29).

¹¹⁶ P. Blach, S. Sambou M'Ban, J. Allard, A. Lemor, Fr. Demande **2014**, FR 3003254A1, 20140919.

¹¹⁷ Y. Usui, K. Sato, M. Tanaka, *Angew. Chem. Int. Ed.* **2003**, 42, 5623-5625.



Scheme 29: Direct dihydroxylation of oleic acid in the presence of the acid resin

2.4.2.2 Enzymatic ring-opening of epoxidized fatty substrates

Besides chemical pathways for the preparation of vicinal diol compounds, enzymatic routes could be an option to avoid the use of external organic acid. In the presence of an epoxy hydrolase enzyme from soy flour, the epoxidized fatty derivatives could be converted to the corresponding diol.¹¹⁸ However, this process requires a long reaction time (100 hours) and is dependent on the substrate. On the one hand, the hydrolysis of epoxidized oleic acid and epoxidized vernolic acid provided a complete conversion after 100 hours. On the other hand, only 73% conversion of epoxidized ricinoleic acid was reached, might be due to the presence of the free OH in this fatty acid derivative. This point indicates the limitation of this enzymatic system for ricinoleic acid and some other similar substrates.

2.5 Hydroformylation

Hydroformylation is an important homologation reaction in organic synthesis because it can introduce one more carbon in the molecular structure as well as introduce a new functionality (carbonyl group). This intermediate could be easily converted to the corresponding acids, amines, alcohols that are very useful in the preparation of surfactants, polyesters, polyurethanes, etc. Considering the importance of hydroformylation, a brief history of this transformation will be given for the fatty derivatives.

2.5.1 Initial result for Co and Rh-based catalysts

The first example of the hydroformylation of fatty substrates was reported by Natta and Beati, using partly “reduced CoO activated” grafted on a betonite material.¹¹⁹ This process occurred at 100-150°C under 20 bar pressure of CO/H₂ and gave a moderate yield for the aldehyde. In 1969, Frankel *et al.* developed an oxo-process, using dicobalt octacarbonyl as a

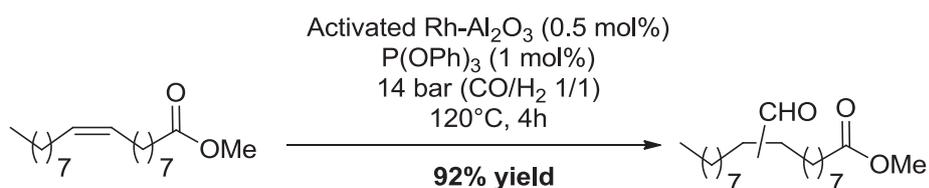
¹¹⁸ G. F. H. Kramer, O. Jurrius, T. C. de Rijk, J. T. P. Derksen, F. P. Cuperus, *Biotechnol. Tech.* **1997**, *11*, 293-295.

¹¹⁹ G. Natta and E. Beati, Britain Patent 646,424, **1950**.

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catalyst.¹²⁰ This hydroformylation was performed under high pressure of syngas (241-315 bar) at 110°C to provide mono-aldehyde products with 42-84% yield, depending on the substrate. However, this method suffers from a lack of yield and selectivity of the desired products (branched/linear/isomerization), over-reduction (alcohol product). Moreover, the Co-catalyst requires harsh conditions for the oxo-process such as an elevated pressure and temperature.

In 1971, an efficient catalytic system for the hydroformylation of methyl oleate was discovered by Frankel, using a Rh-based catalyst in the presence of triphenylphosphine as the ligand.¹²¹ The process was carried out in mild conditions (95-110°C, a 1:1 mixture of CO and H₂, 34-138 bar) and gave an excellent yield (94%) of 9(10)-formyl products. It should be noted that, the presence of phosphine ligand inhibits side reactions such as isomerization and hydrogenation, thus leading to a good yield of 9(10)-oxo products. However, this process still requires a high pressure of syngas (CO/H₂). An optimized condition was developed by Friedrich, using triphenyl phosphite as ligand and an activated supported Rhodium-catalyst.¹²² The hydroformylation was performed at 120°C in the presence of 14 bar of syngas. A nearly complete conversion was observed after 4 hours and a good yield (92%) of formyl products was achieved (Scheme 30).



Scheme 30: Hydroformylation of methyl oleate in the presence of activated Rh-triphenylphosphite

However, Rhodium is one of the most expensive noble metal (ca 1913 euros/ozt,¹²³ more expensive than gold or platinum), so this hydroformylation process should be further developed toward a higher efficiency (lower catalyst loading) and a quantitative recycling of Rhodium catalyst. Recently, there have been many studies investigating the hydroformylation process with a series of different Rhodium precursors such as RhCl₃, Rh(CO)H(PPh₃)₃, Rh(acac)(CO)₂ and different bulky phosphine-based ligands such as DPEphos, BIPHEPHOS, etc.^{124,125,126} In 2014, Borner *et al.* discovered a new hydroformylation process under mild conditions. The reaction was performed with 0.11 mol% of Rh(acac)(CO)₂ as the precursor and phosphoramidite as monodentate phosphorous ligand at 80°C in the presence

¹²⁰ E. N. Frankel, S. Metlin, W. K. Rohwedder, I. Wender, *J. Am. Oil Chem. Soc.* **1969**, *46*, 133-138.

¹²¹ E. N. Frankel, *J. Am. Oil Chem. Soc.* **1971**, *48*, 248-253.

¹²² J. P. Friedrich, *Ind. Eng. Chem. Prod. Res. Dev.* **1978**, *17*, 205-207.

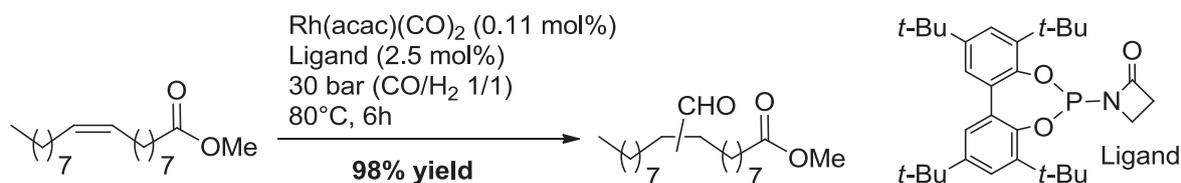
¹²³ <http://www.infomine.com/investment/metal-prices/rhodium/1-month/>, retrieved on 31st May 2018.

¹²⁴ P. Kandanarachchi, A. Guo, Z. Petrovic, *J. Mol. Catal. A: Chem.* **2002**, *184*, 65-71.

¹²⁵ A. N. F. Mendes, J. R. Gregorio, R. G. da Rosa, *J. Braz. Chem. Soc.* **2005**, *16*, 1124-1129.

¹²⁶ Y. Jiao, M. S. Torne, J. Gracia, J. W. H. Niemantsverdriet, P. W. N. M. van Leeuwen, *Catal. Sci. Technol.*, **2017**, *7*, 1404-1414.

of pressurized syngas (30 bar).¹²⁷ The quantitative conversion of methyl oleate was obtained after 6 hours with an excellent yield (98%) of formyl products (Scheme 31).

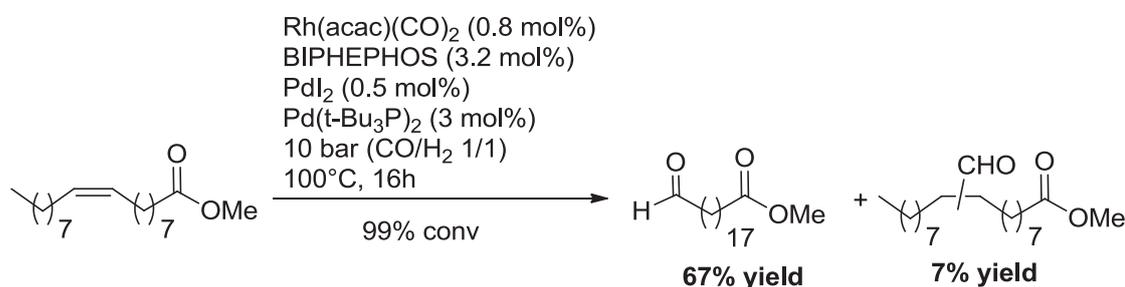


Scheme 31: Hydroformylation process in the presence of Rh/phosphoramidite catalyst

2.5.2 Domino reactions

2.5.2.1 Isomerization-hydroformylation

In 2005, Behr *et al.* discovered a domino isomerization-hydroformylation of methyl oleate.¹²⁸ In the presence of Rh(acac)(CO)_2 and BIPHEPHOS ligand, the sequence reaction was investigated at 125°C under elevated pressure of syngas (10-40 bar). However, only 60% conversion of methyl oleate was obtained and the best yield of ω -oxo substrate (26%) was reached using 10 bar of syngas after 17 hours. Some factors were evaluated to improve the results. On the one hand, increasing the temperature resulted in better conversion but the selectivity declined due to competing hydrogenation reaction. On the other hand, decreasing the temperature favored the generation of branched isomers. It should be noted that rhodium is not a good catalyst for the isomerization process. Then, to favor the production of terminal aldehyde derived from fatty compounds, a bimetallic strategy for isomerization-hydroformylation was developed by Vorholt *et al.*¹²⁹ In this process, a Palladium catalyst was used for the isomerization in combination with a Rhodium catalyst for hydroformylation. A complete conversion of methyl oleate was observed but only 74% yield of aldehyde was achieved with the linear/branched ratio 91/9 (Scheme 32). The rest of the starting material was converted to methyl stearate through hydrogenation.



Scheme 32: Isomerization-Hydroformylation in the presence of bi-metallic catalyst

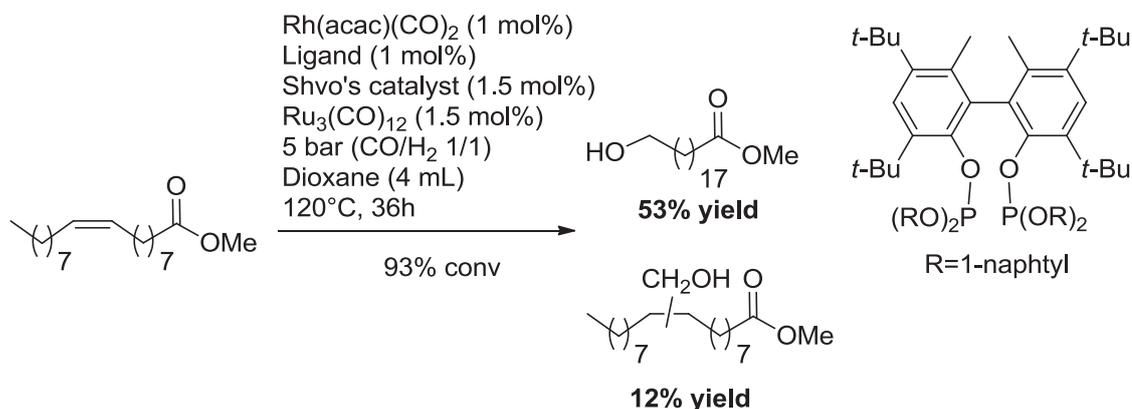
¹²⁷ E. Benetskiy, S. Lühr, M. Vilches-Herrera, D. Selent, H. Jiao, L. Domke, K. Dyballa, R. Franke, A. Börner, *ACS Catal.* **2014**, *4*, 2130–2136.

¹²⁸ A. Behr, D. Obst, A. Westfechtel, *Eur. J. Lipid Sci. Technol.* **2005**, *107*, 213-219.

¹²⁹ T. Gaide, J. Bianga, K. Schlipköter, A. Behr, A. J. Vorholt, *ACS Catal.* **2017**, *7*, 4163-4171.

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In 2013, a complex tandem reaction, so-called isomerization-hydroformylation-hydrogenation, was reported by Nozaki *et al.*, employing a ternary-catalyst system.¹³⁰ By the combination of a mixture of Rh(acac)(CO)₂, bisphosphite ligand and Shvo's catalyst, methyl oleate was converted to the alcohol (67% yield) with a ratio of linear/branched 4.4/1 (Scheme 33). Besides of that, 29% yield of methyl stearate was also obtained as the major by-product for this transformation.



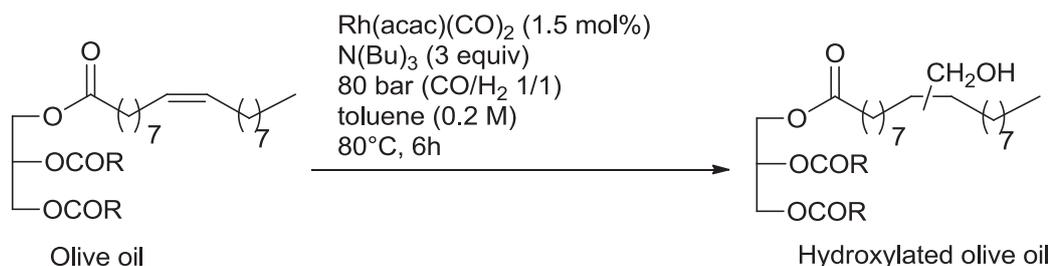
Scheme 33: One-pot access to the linear terminal alcohol from methyl oleate

2.5.2.2 Hydroformylation-hydrogenation

The first attempt for the one-pot, two-reaction hydroformylation-hydrogenation of methyl linoleate was reported by Frankel *et al.*, using a cobalt catalyst.¹²⁰ However, this process requires harsh conditions (250-300 bar of syngas, 180°C, a toxic solvent such as benzene) and gave a good yield (87%) of branched hydroxylated products. Indeed, there are two C=C bonds in methyl linoleate. One double bond was hydrogenated whereas the second one was hydroformylated, followed by hydrogenation to give the mono-hydroxy products. The same procedure was applied to methyl oleate in the presence of tributyl phosphine as a ligand but a low yield (16%) of a linear terminal alcohol derivative was observed due to auto-tandem three-reactions: isomerization-hydroformylation-hydrogenation. Recently, Hapiot *et al.* developed a hydrohydroxymethylation of methyl oleate, employing a Rhodium catalyst and tertiary amine ligand.¹³¹ The domino reaction was performed in smooth conditions (80°C, 80 bar CO/H₂) in toluene. After 6 hours, a nearly quantitative conversion (94%) of olive oil was observed with 90% of hydroxylated products (Scheme 34).

¹³⁰ Y. Yuki, K. Takahashi, Y. Tanaka, K. Nozaki, *J. Am. Chem. Soc.* **2013**, *135*, 17393–17400.

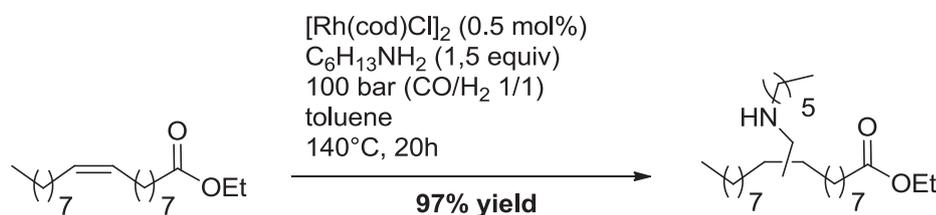
¹³¹ T. Vanbésien, E. Monflier, F. Hapiot, *Green Chem.* **2016**, *18*, 6687–6694.



Scheme 34: Hydrohydroxymethylation of olive oil in the presence of Rh-catalyst

2.5.2.3 Hydroaminomethylation (HAM)

The hydroaminomethylation includes three consecutive reactions: hydroformylation, amine condensation and hydrogenation, to generate an amino fatty compound that could be useful in the production of surfactant or polymer. This domino reaction is often catalyzed by a single rhodium precursor in the presence of amine used as both the ligand and the nucleophilic agent under high pressure of syngas. In 2000, Behr *et al.* have reported the HAM process of ethyl oleate in the presence of primary or secondary amines.¹³² Employing 0.5 mol% of $[\text{Rh}(\text{cod})\text{Cl}]_2$ as the catalyst, the HAM of fatty substrates with aliphatic or aromatic amines provided excellent yields (91-99%) of the desired products (Scheme 35). Moreover, the use of an excess of fatty derivatives (2 equiv) could be converted to bi-functional platforms with a good yield that could be useful in the polymer industry. However, low yield (<5%) were observed with the bulky secondary amine such as diisopropylamine, indicating the limitation of this catalytic system.

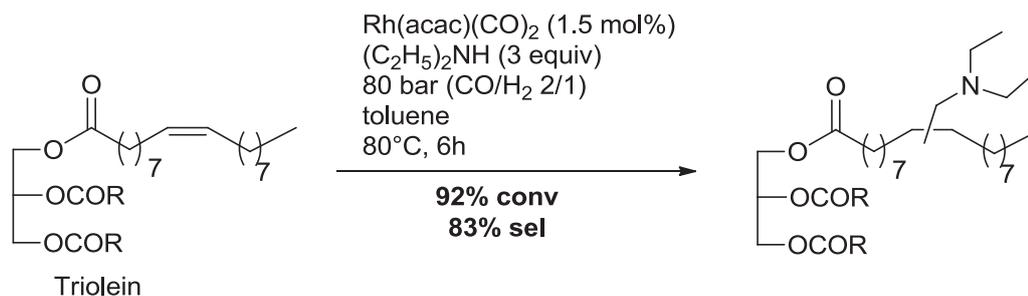


Scheme 35: Hydroaminomethylation of ethyl oleate in the presence of Rh-catalyst

More recently, Hapiot *et al.* reported the HAM process with a secondary amine on a challenging substrate such as triolein.¹³³ The reaction was performed in the presence of Rh(acac)(CO)_2 in toluene at 80°C under high pressure of syngas (80 bar, CO/H_2 2/1). The good conversion (92%) of triolein was observed after 6 hours with a 83% selectivity towards the desired product (Scheme 36). However, this method suffers from a lack of selectivity (the formation of alcohol and hydrogenated products).

¹³² A. Behr, M. Fiene, C. Buß, P. Eilbracht, *Eur. J. Lipid Sci. Technol.* **2000**, 102, 467-471.

¹³³ T. Vanbésien, E. Monflier, F. Hapiot, *Green Chem.* **2017**, 19, 1940-1948.



Scheme 36: HAM of triolein in the presence of a Rh-catalyst

2.5.3 Applications

Herein, we have summarized most of different pathways to incorporate a formyl group onto fatty substrates. Starting from this point, it could be easily converted to polyols (for the traditional production of PUs), polyamines (for the production of NIPUs) and to bifunctional bio-based chemical platforms that could be useful in the synthesis of surfactants and polymers.¹³⁴⁻¹³⁵

2.6 Other transformations

Besides all described transformations, oleochemical derivatives could be converted to a series of useful chemical platforms.¹⁵ For instance, thiol-ene coupling of internal unsaturated fatty compounds with a thiol could give access to a new class of carboxylic acids or alcohols that could be applied to the production of polymers or bio-lubricants.¹³⁶ Hydroalkylation of oleic acid derivative in the presence of aluminum Lewis acid could add one more alkyl group in the chain that helps to modify the physical properties of bio-diesel.¹³⁷

All transformations described in scheme 37 are given in the list below but are not discussed in details.

- a) Thiol-ene coupling reaction^{136,138}
- b) Diels-Alder cycloaddition¹³⁹
- c) Addition of carboxylic acid¹⁴⁰
- d) Hydroalkylation^{137,141}
- e) Nitrile synthesis¹⁴²

¹³⁴ A. Behr, A. J. Vorholt, K. A. Ostrowski, T. Seidensticker, *Green Chem.* **2014**, *16*, 982-1006.

¹³⁵ T. Vanbésien, E. Monflier, F. Hapiot, *Eur. J. Lipid Sci. Technol.* **2016**, *118*, 26–35.

¹³⁶ M. Desroches, S. Caillol, V. Lapinte, R. Auvergne, B. Boutevin, *Macromolecules* **2011**, *44*, 2489-2500.

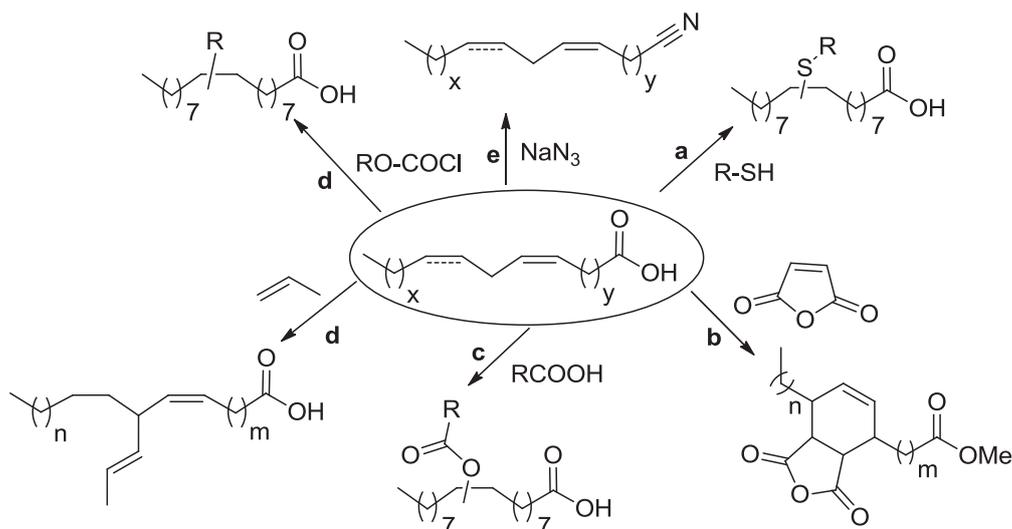
¹³⁷ U. Biermann and J. O. Metzger, *Eur. J. Lipid Sci. Technol.* **2018**, *120*, 1700318.

¹³⁸ O. Türünç, M. A. R. Meier, *Eur. J. Lipid Sci. Technol.* **2013**, *115*, 41-54.

¹³⁹ U. Biermann, W. Butte, T. Eren, D. Haase, J. O. Metzger, *Eur. J. Org. Chem.* **2007**, 3859-3862.

¹⁴⁰ S. C. Cermak, T. A. Isbell, *Ind. Crops Prod.* **2009**, *29*, 205-213.

¹⁴¹ B. Erb, M. Dierker, D. M. Ohlmann, L. J. Gooßen, *Eur. J. Lipid Sci. Technol.* **2016**, *118*, 111-116.



Scheme 37: Other useful transformations of vegetable oil derivatives

3. Cleavage of vegetable oils derivatives

Besides the functionalization of unsaturated fatty substrates, the cleavage of unsaturated vegetable oils and their derivatives is also interesting due to the wide range of applications.¹⁴³ For example, pelargonic acid, obtained from the oxidative ozonolysis of oleic acid, is an herbicide in agriculture. Moreover, the cleavage products can be also converted to higher value-added compounds through chemical transformations. For instance, undecylenic acid obtained through a pyrolytic cleavage of ricinoleic acid, could be used as a starting material for multi-step synthesis of the precursor of Nylon-11. Considering the interest of the cleavage products, the major cleavage processes of oleochemical platforms will be highlighted.

3.1 Thermal cleavage: Retro-ene

Castor oil is one of the most useful vegetable oils that has a variety of nonfood applications such as polyols, polyurethanes or plasticizers. Each year, more than a million ton of castor seeds are produced over the world.¹⁴⁴ There are several unsaturated acids in the composition of castor oil, in which ricinoleic acid ((R,Z)-12-hydroxyoctadec-9-enoic acid) represents from 85-95% of crude castor oil. Except conventional transformations, ricinoleic acid derivatives could be also cleaved to the useful products *via* McLafferty rearrangement.¹⁴⁵

3.1.1 Pyrolysis of ricinoleic acid derivatives

The first thermal cleavage of ricinoleic acid was reported by Genas in 1962.¹⁴⁶ Methyl ricinoleate was obtained through methanolysis of crude castor oil, then the pyrolysis of methyl

¹⁴² C. O.Kangani, B. W.Day, D. E.Kelley, *Tetrahedron Lett.* **2007**, *48*, 5933-5938.

¹⁴³ T. Seidensticker, A. J. Vorholt, A. Behr, *Eur. J. Lipid Sci. Technol.* **2016**, *118*, 3-25.

¹⁴⁴ <https://www.ofimagazine.com/news/castor-seed-production-to-fall-25-in-india-worlds-largest-producer>, retrieved in August 2018.

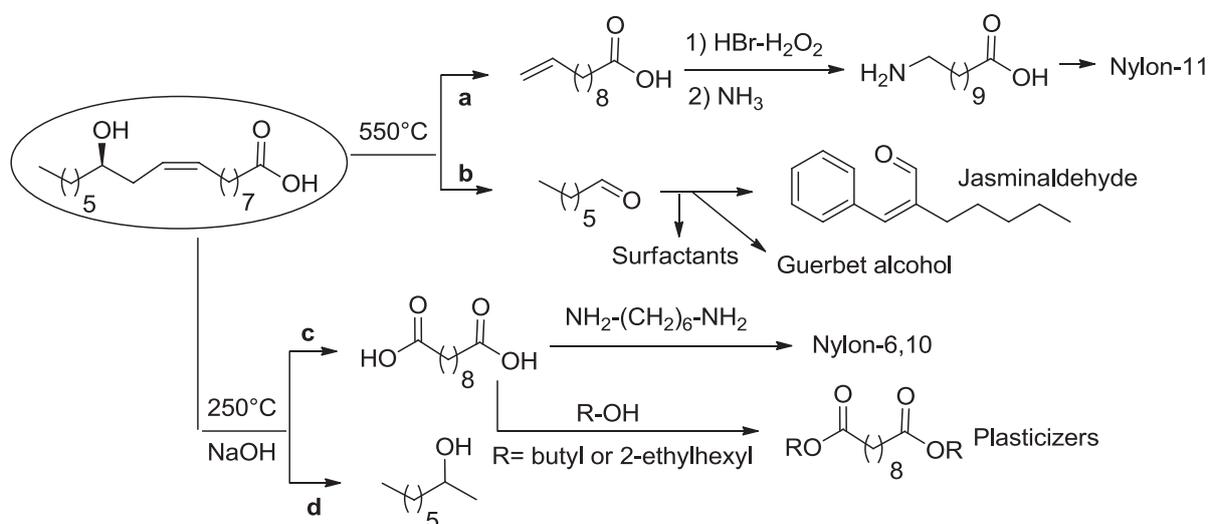
¹⁴⁵ M. Van der Steen and C. V. Stevens, *ChemSusChem* **2009**, *2*, 692-713.

¹⁴⁶ M. Genas, *Angew. Chem.* **1962**, *74*, 535-540

ricinoleate was investigated at 550°C to provide an overall 75% yield of heptanal and undecylenic acid (Scheme 38, route a and b). This intermediate was converted to 11-aminoundecanoic acid through hydrobromination and amination, that can be polymerized to Nylon 11 (Scheme 38, route a). The co-product heptanal can be used for the synthesis of fragrances (jasminaldehyde, etc), guerbet alcohols or surfactants (Scheme 38, route b).¹⁴⁷ For example, heptanal could be reduced to heptanol,¹⁴⁸ that was used to prepare heptyl glucoside as a 100% bio-based surfactants.

3.1.2 Alkaline thermal cleavage of ricinoleic acid.

The thermal decomposition of ricinoleic acid was investigated in alkaline medium at elevated temperature (180°-250°C) (Scheme 38, route c and d).¹⁴⁹ In the presence of NaOH as the catalyst, sebacic acid (C10) was obtained with a moderate yield (67%), together with ω-hydroxy fatty acid (19%). The C10-diacid was condensed with 1,6-diaminohexane for the production of the nylon-6,10. Moreover, dialkyl sebacates such as dibutyl sebacate and di-2-ethylhexyl sebacate could be used as plasticizers (Scheme 38, route c). Additionally, 2-octanol was also obtained as the co-product of alkaline fusion and was used in a variety of applications such as flavor, low-volatile solvent or defoaming agent in the production of pulp and paper (Scheme 38, route d).¹⁵⁰



Scheme 38: Thermal decomposition of ricinoleic acid at elevated temperature

3.2 Olefin metathesis

Olefin metathesis is the most attractive and powerful methods for the formation of α -olefins from internal alkenes in organic and polymer chemistry. At the beginning, this reaction

¹⁴⁷ M. Perez-Sanchez, P. D. de Maria, *Catal. Sci. Technol.* **2013**, 3, 2732-2736.

¹⁴⁸ The SEPPIC company received the medal of the Pierre Potier prize in 2013 for chemistry innovation for sustainable development, for launching heptyl glucoside, a 100%-biobased solubilizer.

¹⁴⁹ M. J. Diamond, R. G. Binder, T. H. Applewhite, *J. Am. Oil Chem. Soc.* **1965**, 42, 882-884.

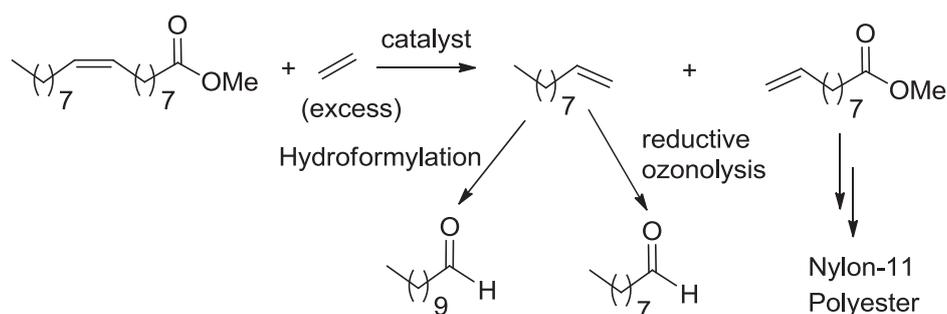
¹⁵⁰ F. C. Naughton, *J. Am. Oil Chem. Soc.* **1974**, 51, 65-71.

was catalyzed by tungsten or molybdenum catalysts.¹⁵¹ However, these methods suffered from a low of selectivity and required high amount of catalyst. In 1996, a highly active, stable and chemically tolerant catalyst based on a ruthenium-carbene complex was innovated by Grubbs *et al.*¹⁵² Then, numerous transformations of chemical platforms were developed to make new interesting platforms as well as fragmented the polymers based on olefin metathesis. In fact, the metathesis catalysts usually favor the formation of *E*-isomers, but recently Hoveyda *et al.* reported that the generation of *Z*-selective products is possible using a very bulky catalyst.¹⁵³ Even if this catalyst exhibits a really high TON but the homogeneous Ru-catalyst should be immobilized on insoluble materials which have high surface areas, large pores or narrow pore size distribution.¹⁵⁴ In this context, we will only focus on the cleavage of unsaturated fatty substrates using Ruthenium carbene catalyst, including cross-metathesis, self-metathesis and ring-closing metathesis.

3.2.1 Cross-metathesis

3.2.1.1 Cross-metathesis with ethylene

The interest for the ethenolysis of unsaturated vegetable oils lies on the uses of cleavage products. For example, methyl dec-9-enoate could be used as a key intermediate in the production of the Nylon-11, other polyesters and for the preparation of bioactive compounds such as the prostaglandin. Additionally, the co-product decene-1 could be employed for synthesis of the fatty aldehydes, the fatty acids *via* hydroformylation or oxidative cleavage process, that have a broad range of applications in the production of the surfactants, estolides or polymers (Scheme 39).



Scheme 39: Cross-metathesis of methyl oleate and ethylene

An initial attempt on the metathesis of methyl oleate and ethylene was reported by Mol *et al.*, using WCl_6/Me_4Sn or $Re_2O_7/Al_2O_3/Me_4Sn$ as catalytic system.¹⁵⁵ However, the reaction provided moderate conversion (57-85%) and low selectivities of the terminal olefin

¹⁵¹ E. A. Zuech, W. B. Hughes, D. H. Kubicek, E. T. Kittleman, *J. Am. Chem. Soc.* **1970**, *92*, 528–531.

¹⁵² R. Grubbs, S. B. T. Nguyen, L. Johnson, M. A. Hillmayer, C. F. U. Gregory, WO1996004289A1.

¹⁵³ M. J. Koh, R. K. M. Khan, S. Torke, M. Yu, M. S. Mikus, A. H. Hoveyda, *Nature* **2015**, *517*, 181–186.

¹⁵⁴ J. Bidange, C. Fischmeister, C. Bruneau, *Chem. Eur. J.* **2016**, *22*, 12226 – 12244.

¹⁵⁵ R. H. A. Bosma, F. Van den Aardweg, J. C. Mol, *J. Chem. Soc., Chem. Commun.* **1981**, *0*, 1132-1133.

derivatives (57-85%), caused by the formation of the self-metathesis compounds as the major by-products.

Recently, the development of Ru-based catalysts has gained more interest after the innovation of Grubbs.¹⁵² Several modifications of the chemical structure of the ligand were carried out toward higher stability of the catalyst as well as better performance (TON). Moreover, some of Grubbs catalysts are commercially available and have a wide range of applications in the transformation of oleochemical platforms and fossil-based feedstocks (Figure 4).

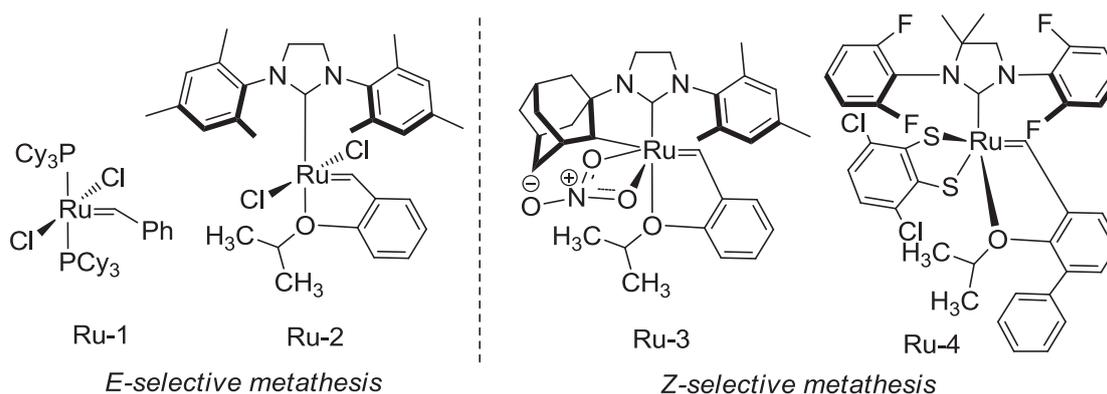


Figure 4: Selective Ruthenium catalyst for olefin metathesis, adapted from ref 156

In particular, several factors should be considered to obtain good results for ethenolysis.¹⁵⁷ First of all, the purity of (bio)-ethylene should be more than 99.95% because of the presence of impurities such as carbon monoxide or acetylene that could poison or limit the reactivity of the catalyst. Secondly, a green solvent such as dimethyl carbonate could be used to avoid the formation of homometathesis products. Initially, the ethenolysis was often performed in neat conditions. However, the reaction suffered from the generation of self-metathesis products. The use of toluene could eliminate the formation of these by-products, but toluene is a toxic solvent. Then, the seeking of alternative solvents is also important to reach a greener process.¹⁵⁸

Other factors that should be considered are the temperature and pressure of ethylene. On the one hand, the ethenolysis was often carried out in moderate temperature between 40-70°C to decrease the viscosity of the substrates, improve the solubility of ethylene as well as avoid the degradation of the catalyst. On the other hand, the increase of ethylene pressure could improve the reactivity of the catalysts. For instance, the conversion of methyl oleate, using a Grubbs-1st generation catalyst (200 ppm), reached 82% in the presence of 16.5 bar ethylene, while only 56% conversion was obtained in the presence of 1 bar of ethylene. Finally, the chemical decomposition of catalysts should be also considered. For

¹⁵⁶ O. M. Ogba, N. C. Warner, D. J. O'Leary, R. H. Grubbs, *Chem. Soc. Rev.* **2018**, 47, 4510-4544.

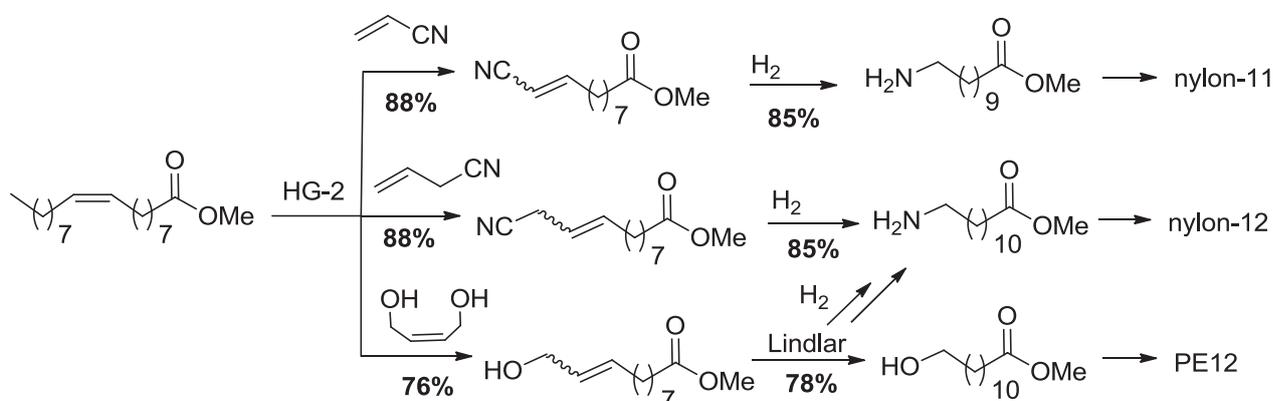
¹⁵⁷ J. Spekrijse, J. P. M. Sanders, J. H. Bitter, E. L. Scott, *ChemSusChem* **2017**, 10, 470-482.

¹⁵⁸ T. P. Montgomery, A. M. Johns, R. H. Grubbs, *Catalysts* **2017**, 7, 87-125.

example, *N*-methyl morpholine as a stabilizing in toluene could substitute the phosphine ligand in Ruthenium catalyst, causing a decrease of the reactivity. Moreover, the Ru-based catalyst could be subjected to metathesis with ethylene to generate unstable ruthenium methylidene species, leading a decrease of the lifetime of the catalyst. Then the search of an highly active stable catalyst for metathesis is still highly demanded.

3.2.1.2 Cross-metathesis with nitrile or hydroxyl derivatives

Since the discovery of metathesis catalysts, numerous works to valorize fatty acid substrates into high value-added compounds have been reported. One of the most interesting pathway is the cross-metathesis of methyl oleate with functional compounds such acrylonitrile, fumaronitrile or *cis*-butene-1,4-diol (Scheme 40).¹⁵⁹ In the presence of Grubbs-Hoveyda 2nd generation (Ru-2, 1 mol%, figure 4) and benzoquinone as an isomerization inhibitor, the reaction gave a quantitative conversion of methyl oleate after 2.5 hours at 110°C. A mixture of *Z/E*-isomers was observed as the major product of the metathesis reaction (containing more than 88% *Z*-isomer, that is an opposite trend compared with the ethenolysis or self-metathesis of methyl oleate. These intermediates could be reduced under pressurized hydrogen and metal catalyst to key precursors for the production of Nylon-11 and Nylon-12. Moreover, the bi-functionalized hydroxy-ester could also be converted to polyamide precursors through multi-step synthesis or reduced to the corresponding ω -hydroxy fatty acid derivative that could be polymerized to give polyesters.



Scheme 40: Cross-metathesis of methyl oleate with nitrile or hydroxyl derivatives

3.2.2 Self-metathesis

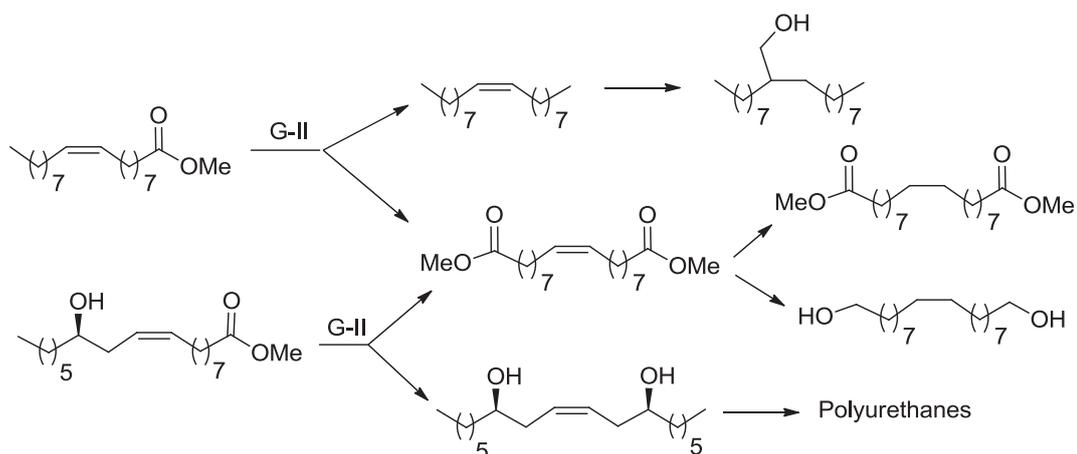
One of the first investigations on the self-metathesis of methyl oleate or other fatty substrates was studied by Mol and Dinger.¹⁶⁰ Using the Grubbs 2nd generation catalyst, the homo-metathesis of methyl oleate at 55°C gave a good selectivity for the desired products (91%) and an unexpected high turnover number (440000). However, only 45% conversion of methyl oleate was observed, indicating the limitation of this metathesis reaction. A similar

¹⁵⁹ K. Yamamoto, S. Viamajala, S. Varanasi, K. Nguyen, G. Abel, Y. Mudiyanselege, US20170204051A1.

¹⁶⁰ M. B. Dinger and Johannes C. Mol, *Adv. Synth. Catal.* **2002**, 344, 671-677.

work was also reported by Foglia *et al.* In the presence of catalytic amount of the 2nd generation Grubbs catalyst (0.1 mol%), the self-metathesis of methyl oleate at 45°C provided a moderate conversion (50%) with a 39% isolated yield of the diester product after 3 days.¹⁶¹ More interestingly, the self-metathesis of oleic acid in the same condition gave a good yield of the diacid derivatives (71%). However, a mixture of two isomers (Z/E) was obtained, indicating the lack of stereoselectivity for this transformation. Toward the remaining of configuration of the starting material and faster initiation, the new generation of catalyst was designed by Grubbs and Ahmed.¹⁶² In the presence of 0.1 mol% of a dithiolate catalyst (Ru-4, figure 4), the self-metathesis of methyl oleate or methyl elaidate in THF at room temperature gave a moderate conversion (50%) after 20 or 50 minutes. More interestingly, the stereoselectivity of the desired products reached 99% for only the Z or E-isomer. It should be noted that the self-metathesis products are interesting in term of applications. On the one hand, the dioleic acid is a whitening component in cosmetic.¹⁶³ On the other hand, further reduction of unsaturated diester or diacid gives the corresponding saturated diester or α,ω -diol that are both useful in the production of polyesters (Scheme 40).¹⁶⁴

Other interesting oleochemical platforms could be obtained from the homo-metathesis of methyl ricinoleate that represents more than 85% in castor oil. Using Grubbs-II as the catalyst (Figure 4, Ru-2), the self-metathesis of methyl ricinoleate in ionic liquid at 60°C gave a conversion of 60% after 4 hours and an excellent selectivity toward the desired products (99%). Furthermore, the expensive catalyst could be recycled and reused without any loss of activity. Otherwise, the self-metathesis products of methyl ricinoleate are attractive intermediates for the preparation of diacids, diols (*via* reduction),thiol-ene coupling in the production of polyesters or polyurethanes (Scheme 41).¹⁶⁵



Scheme 41: Self-metathesis of fatty acid derivatives in the presence of Grubbs-II catalyst

¹⁶¹ H. L. Ngo, K. Jones, T. A. Foglia, *J. Am. Oil Chem. Soc.*, **2006**, *83*, 629-634.

¹⁶² T. S. Ahmed, R. H. Grubbs, *J. Am. Chem. Soc.* **2017**, *139*, 1532–1537.

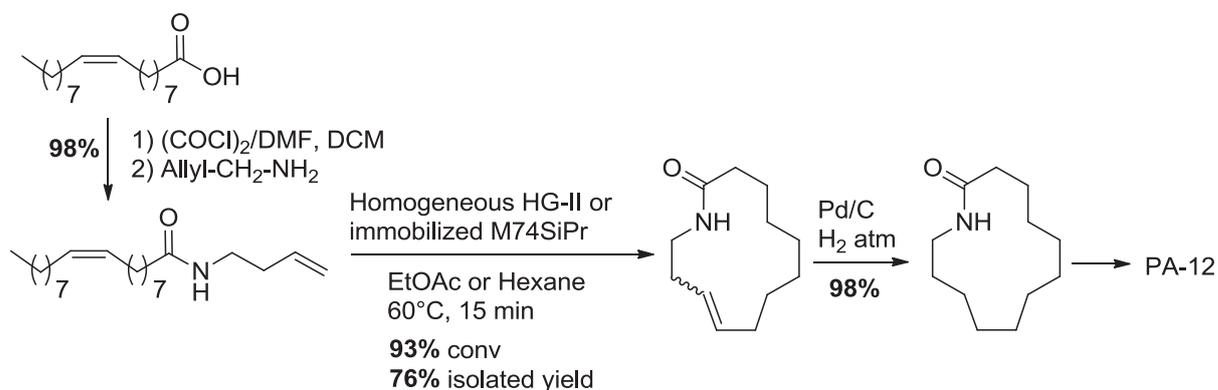
¹⁶³ J. Allard, S. Sambou, M. Mauduit, F. Caijo, F. Tripoteau, WO2016083735A1.

¹⁶⁴ A. Gonzalez-de-Castro, E. Cosimi, M. J. B. Aguilá, P. Gajewski, M. Schmitkamp, J. G. de Vries, L. Lefort, *Green Chem.* **2017**, *19*, 1678–1684.

¹⁶⁵ P. A. Thomas, B. B. Marvey, E. E. Ebenso, *Int. J. Mol. Sci.* **2011**, *12*, 3989-3997.

3.2.3 Ring-closing metathesis

The first investigation on the synthesis of PA-11 or PA 12 precursors based on the ring-closing metathesis was reported by Yamamoto *et al.* in 2014.¹⁶⁶ The process occurred in three-steps, including the amidation of oleic acid, ring-closing metathesis and reduction with a good yield for each step (Scheme 42). The key step in this consecutive reaction is the ring-closing metathesis, using the Hoveyda-Grubbs II (2 mol%). The reaction was examined using chlorobenzene as solvent at 120°C for 30 min. A nearly complete conversion (97%) was observed with a 71% yield of the ene-lactame product. The major by-product was the oligomer products (10%), coming from ring-opening metathesis of the ene-lactame. However, this reaction was carried out in chlorinated solvent at an elevated temperature that could degrade the catalyst. Toward a greener process, Yamamoto *et al.* also reported a modification with several advantages such as a lower temperature (60°C), a shorter reaction time (15 minutes), using the heterogenized catalyst and a greener solvent (EtOAc).¹⁶⁷ To make it, the HG-II-type catalyst (M74SiPr) was grafted onto high surface area of mesoporous silica (such as MCM-41, SBA-15). Using these catalysts, the reaction provided an excellent conversion (93%) in only 15 minutes with a good isolated yield (76%) of the desired product (Scheme 42). Moreover, these catalysts could be recycled and reused at least three times without any significant loss of activity.



Scheme 42: Synthesis of the precursors of polyamide, based on the ring-closing metathesis process

3.3 Cleavage of vicinal diol to the acids

There are a variety of methods to cleave vicinal fatty diols into two carboxylic acids, using a stoichiometric amount of oxidant such as KMnO₄, NaIO₄, hydrogen peroxide, bleach, oxygen, etc. However, the utilization of non-green oxidants such as KMnO₄ or NaIO₄ requires a slight excess of reagent.¹⁶⁸ Moreover, the process generates a large quantity of wastes (MnO₂, NaIO₃), causing to difficult purification of the desired products. In the context of green chemistry, we

¹⁶⁶ A. Y. Mudiyansele, S. Viamajala, S. Varanasi, K. Yamamoto, *ACS Sustainable Chem. Eng.* **2014**, 2, 2831–2836.

¹⁶⁷ G. A. Abel, S. Viamajala, S. Varanasi, K. Yamamoto, *ACS Sustainable Chem. Eng.* **2016**, 4, 5703–5710.

¹⁶⁸ H. R. Le Seur, *J. Chem. Soc., Trans.* **1901**, 79, 1313–1324.

only describe the oxidative cleavage of vicinal diols, using green oxidants such as hydrogen peroxide, NaOCl solution or oxygen.

3.3.1 Oxygen

Oxygen is the cheapest and the most abundant oxidizing agents for the cleavage of vicinal diols. Only water is a by-product from this oxidation process. However, the use of molecular oxygen alone is not selective and leads to a low carbon balance. That is the reason why, a catalytic amount of metal complexes is required to obtain better performances.

At the beginning, Cobalt (II) acetate was one of the best candidates for this kind of transformation. In 1972, Schreyer *et al.* claimed that in the presence of Cobalt salt (0.16 mol%), the oxidative cleavage of oleic acid diol in AcOH at 50°C provided a good conversion.¹⁶⁹ Moreover, a good yield of pelargonic (86%) and azelaic acid (82%) was achieved after distillation. A similar work was reported by Nakazawa *et al.* in 1984.¹⁷⁰ The cleavage of oleic acid diol was investigated in the presence of a mixture of Co(OAc)₂ (5 mol%) and Mn(OAc)₂ (2.5 mol%), using 5 bar of oxygen. The reaction was performed at 100°C for 30 minutes to give a good yield of two corresponding fatty acids (68% for pelargonic acid, 81% for azelaic acid). In 2011, a modified process was studied by Bierser *et al.*¹¹⁵ The cleavage of polyol vegetable oil was investigated in continuous flow of cobalt, using air as an oxidant. In the presence of certain amount of Co(OAc)₂ (0.4 mol%), the reaction was conducted at 72°C in high pressure of air (22 bar, equivalent 2.5 bar of oxygen) for 5 hours. A good yield (70%) of pelargonic acid was isolated after this process. Then, the hydrolysis of the triglyceride was examined in acidic medium using Amberlyst to give a good yield of azelaic acid (73%) (Scheme 43). Recently, a C-C cleavage of vicinal diol from methyl oleate was also investigated in semi-continuous miniplant scale.¹⁷¹ The reaction was conducted in AcOH at 100°C, using Co(acac)₂ and *N*-hydroxy phthalimide (NHPI) as promoters and molecular oxygen as an oxidant. After 6 hours, pelargonic and mono methyl azelate were obtained in a yield of 68% and 66%, respectively.



Scheme 43: Oxidative cleavage of polyol sunflower oil in continuous flow

In 2011, Lemaire *et al.* described an oxidation process of methyl oleate diol, using a ruthenium hydroxy supported on alumina as the catalyst (1 mol%).¹⁷² The reaction was

¹⁶⁹ G. Schreyer, W. Schwarze, W. Weigert, H. Weigel, Patent N° DE 2106913, **1972**.

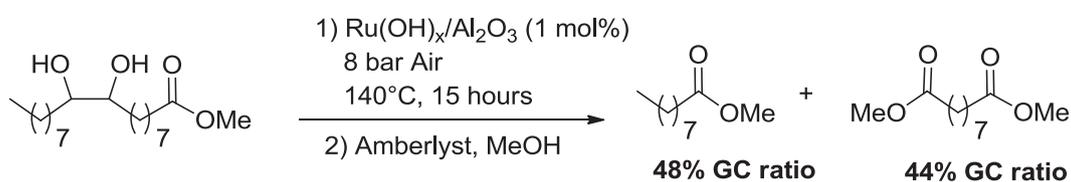
¹⁷⁰ M. Nakazawa, K. Fujitani, H. Manami, Patent N° EP 128484, **1984**.

¹⁷¹ A. Behr and N. Tenhumberg, *Chem. Ing. Tech.* **2012**, *84*, 1559-1567.

¹⁷² M. Lemaire, E. Metay, M. Sutter, J. Debray, Y. Raoul, N. Duguet, Patent N° US9359280B2.

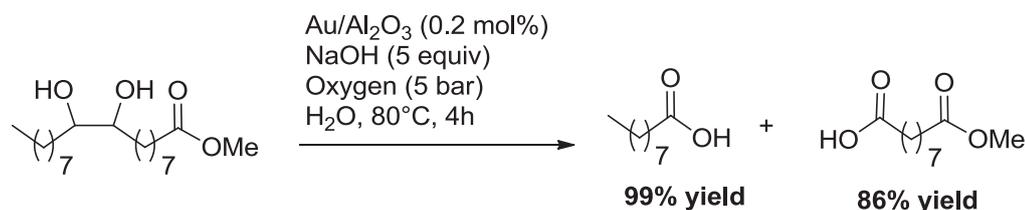
CHAPTER I: VEGETABLE OIL

conducted in pressurized air (8 bar) at 140°C for 15 hours. A mixture of products was esterified with methanol in the presence of Amberlyst to give a good yield of the corresponding fatty acid methyl esters (48% for methyl pelargonate and 44% for dimethyl azelate as determined by GC) (Scheme 44). A small portion of dimethyl sebacate and methyl caprylate was identified as the unwanted products from this cleavage.



Scheme 44: Oxidative cleavage of methyl oleate diol in the presence of $\text{Ru(OH)}_x\text{-Al}_2\text{O}_3$

More recently, Kockritz *et al.* have developed an efficient catalytic system, using an heterogeneous system based on gold.¹⁷³ The gold species was supported on alumina, then was applied as the catalyst for this transformation. The reaction was conducted in the presence of oxygen (5 bar) in a strong basis aqueous solution at 80°C and provided in a high yields of pelargonic acid (99%) and azelaic acid (86%) (Scheme 45). Moreover, the catalyst was easily separated through filtration and re-used at least 5 times without significant loss of activity.



Scheme 45: Cleavage of dihydroxylated fatty substrate in the presence of gold catalyst

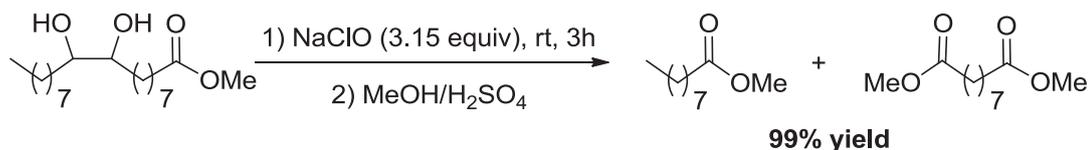
3.3.2 Bleach

In 2009, Lemaire *et al.* claimed that a quantitative formation of two corresponding fatty acids was achieved when a excess of bleach (3.2 equiv) was used for the oxidative cleavage of methyl 9,10-dihydroxyoctadecanoate in neat conditions at room temperature (Scheme 46).^{174,175} Moreover, these conditions were applied to other fatty diols derived from oleic acid, dioleic acid, ricinoleic acid or linoleic acid. These intermediates were next esterified with methanol in acidic condition to give the corresponding fatty methyl ester with good yields (53-89%), indicating the versatility of this method. However, this method involves the leaching of chlorine anion and forms an important quantity of co-product (NaCl), showing the limitation of the use of bleach for this transformation.

¹⁷³ A. Kulik, A. Janz, M.-M. Pohl, A. Martin, A. Kockritz, *Eur. J. Lipid Sci. Technol.* **2012**, 114, 1327–1332.

¹⁷⁴ PhD thesis, Melle PAQUIT Bénédicte, Université de Lyon, **2009**.

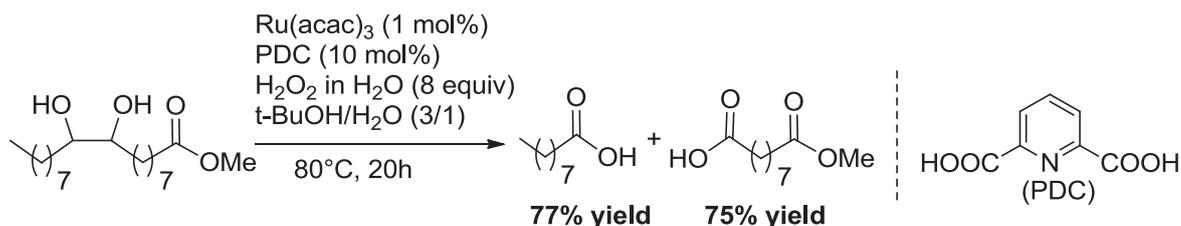
¹⁷⁵ M. Lemaire, A. Favre-Reguillon, B. Paquit, S. Claude, Y. Raoul, Patent N° US20130131379A1.



Scheme 46: Oxidative cleavage of vicinal fatty diol in the presence of bleach

3.3.3 Hydrogen peroxide

Hydrogen peroxide is also a cheap and promising oxidant for oxidative cleavage of diol derivatives. In comparison with bleach, it is even better because it contains a higher oxygen content than bleach (Table 1) and only water is a co-product. In fact, the cleavage of diol could be performed in the presence of hydrogen peroxide only but a low conversion and a lack of selectivity of desired products were observed, then a catalytic amount of the metal and ligand was applied to increase the kinetics of the reaction and reactivity of the cleavage. One of the efficient methods, using Ru-based catalyst was reported by Behr *et al.* (Scheme 47).¹⁷⁶ In the presence of Ru(acac)₃ and dipicolinic acid (PDC), the cleavage of methyl 9,10-dihydroxystearate at 80°C provided an outstanding conversion (99%) and pelargonic acid and monomethyl azelate were obtained with 77% and 75% yield, respectively.



Scheme 47: Oxidative cleavage of vicinal fatty diol in the presence of hydrogen peroxide

3.3.4 Applications

Pelargonic acid and its derivatives have a wide range of applications. In fact, there are three major pathways to access this compound: i) the oxidation of nonanal that was prepared *via* hydroformylation of 1-octene, ii) the oxidative ozonolysis of methyl oleate and iii) the oxidative cleavage of methyl oleate or dihydroxylated methyl oleate catalyzed by a metal species in the presence of air or oxygen. Among them, the third route is the dominant one with an available starting material, cheap catalyst and simple process, contrary to the two first, that required a special equipment, highly intensive energy process (ozonolysis) or derived from the cracking product of fossil materials. In 2012, the total consumption of nonanoic acid was approximately 3×10^4 tons for a variety of applications.¹⁷⁷ Firstly, pelargonic acid is considered as a bio-herbicide, not only for grass weeds but also for annual and perennial broadleaf. Secondly, pelargonic acid is used for the preparation of value-added compounds. For instance, nonivamide, that is a condensation product between vanillylamine and pelargonic acid, is used

¹⁷⁶ A. Behr, N. Tenhumberg, A. Wintzer, *RSC Adv.* **2013**, *3*, 172–180.

¹⁷⁷ J. Kubitschke, H. Lange, H. Strutz, *Ullmann's Encyclopedia of Industrial Chemistry*, DOI: 10.1002/14356007.a05_235.pub2

in the production of food additives such as flavoring, seasoning or spice blend. On the other side, neopolyol pelargonate is considered as a green lubricant and fluid for gas turbines because of its good thermal stability and oxidation resistance. Otherwise, nonanoyloxybenzenesulfonate (NOBS) was developed in 1983 by P&G and was used as a bleach activator for superior performance in low-temperature laundry detergents.^{178,179}

Azelaic acid is a bio-dicarboxylic acid and could be found in a small content in many natural substances. Previously, the main production of this diacid was originated from oxidative ozonolysis process of oleic acid.¹⁸⁰ However, this reaction involves with the generation of ozone that is the highly energy-intensive. More recently, azelaic acid was considered as the co-product from oxidative cleavage of oleic acid in the presence of air and metal.¹¹⁵ This dicarboxylic acid is also used in a variety of applications.¹⁸¹ Firstly, azelaic acid was used directly in pharmacy for the treatment of acnes. Moreover, azelaic acid is an important precursor for synthesis of higher value-added compounds. For instance, di 2-ethylhexyl azeleate is used as a plasticizer. The other dialkyl azeleates with a fatty alcohol such oleyl alcohol are used as bio-lubricants. Finally, nylon-6,9 that is a condensation product between azelaic acid and hexamethylene diamine, is used as an extrude film for food packaging or as coating for wire.

3.4 Ozonolysis

Ozonolysis has been a powerful method for the cleavage of unsaturated fatty acids to oxo-products. It was mainly used for the production of pelargonic acid and azelaic acid from oleic acid. This reaction uses ozone that is a toxic and explosive gas even in a small quantity. Moreover, the generation of ozone is a highly intensive-energy process and requires special equipments. From a mechanistic point of view, the ozonisation process involves preliminary formation of ozonides. Otherwise, this reaction also generates other tetraoxanes (secondary ozonides) that are unstable and highly explosive intermediates.¹⁸² There are two strategies to access the final fatty derivatives from these ozonides: oxidative ozonolysis to fatty acids¹⁸³ or reductive ozonolysis to fatty aldehydes.¹⁸⁴

3.4.1 Oxidative ozonolysis

The oxidative ozonolysis of oleic acid was reported by Ackman *et al.* in 1961.¹⁸³ The reaction was conducted in methanol at low temperature (-30°C) in the presence of ozone to

¹⁷⁸ S. Y. Chung, G. L. Spadini, Patent N° US4412934, **1983**.

¹⁷⁹ H.G. Hauthal, *Tenside Surf. Det.* **2012**, *49*, 171–177.

¹⁸⁰ C. G. Goebel, A. C. Brown, H. F. Oehlschlaeger, R. P. Roelfes, Patent N° US2812113, **1957**.

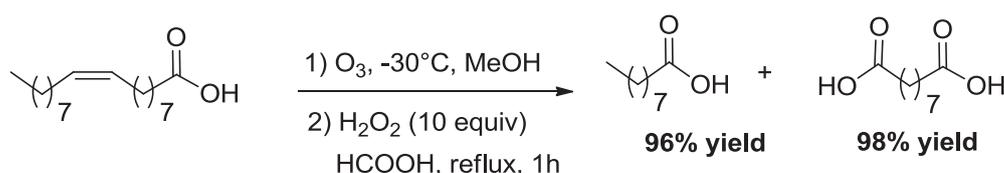
¹⁸¹ B. Cornils and P. Lappe, Ullmann's Encyclopedia of Industrial Chemistry, DOI: 10.1002/14356007.a08_523.pub3.

¹⁸² M. B. Rubin, *Helv. Chim. Acta.* **2003**, *86*, 930–940.

¹⁸³ R. G. Ackman, M. E. Retson, L. R. Gallay, F. A. Vandenheuvel, *Can. J. Chem.* **1961**, *39*, 1956–1963.

¹⁸⁴ K. Louis, L. Vivier, J.-M. Clacens, M. Brandhorst, J.-L. Dubois, K. D. O. Vigier, Y. Pouilloux, *Green Chem.* **2014**, *16*, 96–101.

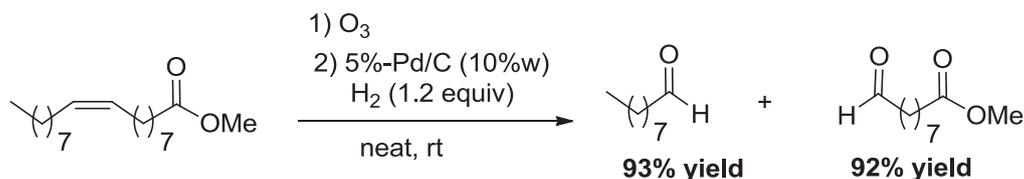
form the primary ozonide intermediates. The oxidative step was performed in the presence of hydrogen peroxide and formic acid and provided a good yield of pelargonic acid (96%) and azelaic acid (98%) (Scheme 48). This study also mentioned that reaction medium has an important role for the formation of final products. On the one hand, polar solvents such water, methanol or AcOH favor the generation of peroxide and carbonyl products. On the other hand, non-polar solvents and chlorinated solvents promote to form the ozonide intermediates that could be isolated and converted to other family of compounds. This process was the major procedure in the industrial production of nonanoic acid and azelaic acid before the invention of the NOVAMONT process.^{115,180}



Scheme 48: Oxidative ozonolysis of oleic acid in the presence of hydrogen peroxide

3.4.2 Reductive ozonolysis

The reductive ozonolysis of oleic acid is an efficient cleavage to approach bio-aldehydes such as nonanal and methyl azelaaldehyde. Initially, this reduction reaction was conducted in the presence of zinc/AcOH or dimethyl sulfide or triaryl phosphine and gave good yields of the aldehydes (90-92%). However, the drawback of this reaction is the lack of selectivity (Zn/AcOH)¹⁸⁵ or the purification process (Ph₃P/Ph₃PO).¹⁸⁶ More recently, Louis *et al.* developed mild conditions to reduce ozonide intermediates into two aldehydes.¹⁸⁴ The reaction was conducted in solvent-free condition at room temperature in the presence of heterogeneous catalyst Pd/C and hydrogen pressure to give two aldehydes with high yields (Scheme 49). Moreover, the catalyst Pd/C was easily separated through filtration and re-used at least 9 times without loss of activity.



Scheme 49: Reductive ozonolysis of methyl oleate in the presence of Pd-catalyst

3.5 Biocatalytic cleavage

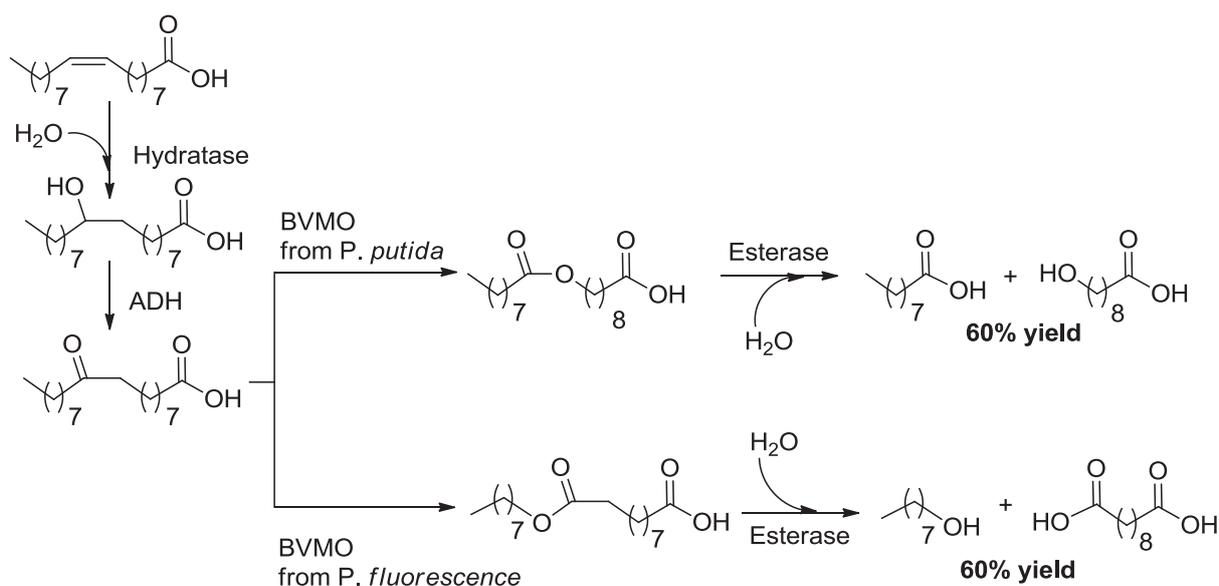
Recently, the enzymatic cleavage has become a new trend in organic synthesis. Even if this transformation is working well using traditional chemical methods, the conditions often require a high temperature or a large amount of catalyst. Moreover, enzymatic oxidation often works with

¹⁸⁵ C. R. Noller and R. Adams, *J. Am. Chem. Soc.* **1926**, *48*, 1074-1080.

¹⁸⁶ Y. S. Hon and K. C. Wu, *Tetrahedron*, **2003**, *59*, 493-498.

hydrophilic substrates such as carbohydrates. In this context, we describe the enzymatic cleavage that could be applicable to oleochemical platforms.

Actually, one of the first enzymatic oxidation of fatty acid derivatives involves the ω -oxidation of fatty acids and was applied for the preparation of monomers such as fatty diacid for the production of bio-plastics.¹⁸⁷ More recently, a study from Park *et al.* shows that an α,ω -fatty dicarboxylic could be synthesized *via* cleavage of fatty substrates, using a multi-enzymatic system.¹⁸⁸ Indeed, the first model for this tandem reaction was a hydroxylated fatty acid such as ricinoleic acid and the combination of three enzymes was applied. Among them, an alcohol dehydrogenase (ADH) was used for the oxidation of secondary alcohol to corresponding ketone, a Bayer-Villiger monoxygenase (BVMO) was involved for the oxidation of ketone to the fatty ester, then an esterase was used for the hydrolysis of the esters to access to heptanoic acid and ω -hydroxyl fatty acid with good yields (70%) which could be used as a bio-monomer or further oxidized to an α,ω -dicarboxylic acid.¹⁸⁷ Otherwise, for other unsaturated fatty acids, the use of another enzyme such as a hydratase was required to convert unsaturated fatty compounds to hydroxylated substrates (Scheme 50). Interestingly, there are two options for the Bayer-Villiger enzymatic oxidation and the use of enzymes is depended on their targets.



Scheme 50: Consecutive enzymatic transformation to access novel monomer platforms

3.6 Conclusion

Herein, we have summarized most the major pathways to cleave oleochemical platforms. Fatty aldehydes and fatty acids are considered as the dominant products from the cleavage process and are used for a wide range of applications such as herbicides, pharmaceuticals as well

¹⁸⁷ W. Lu, J. E. Ness, W. Xie, X. Zhang, J. Minshull, R. A. Gross, *J. Am. Chem. Soc.* **2010**, *132*, 15451–15455.

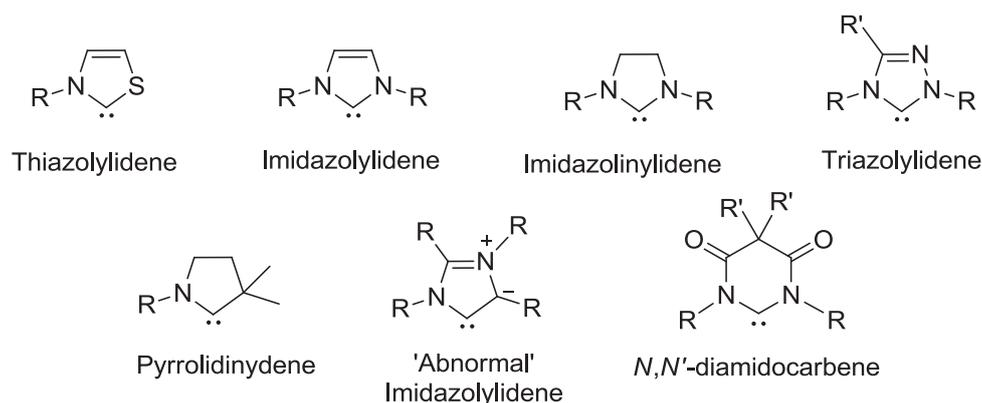
¹⁸⁸ J.-W. Song, E.-Y. Jeon, D.-H. Song, H.-Y. Jang, U. T. Bornscheuer, D.-K. Oh, J.-B. Park, *Angew. Chem. Int. Ed.* **2013**, *52*, 2534–2537.

as the preparation of higher value-added compounds such as surfactants, plasticizers and polymers.

4. N-Heterocyclic carbenes (NHCs)

4.1 Overview

N-heterocyclic carbenes (NHCs) are currently playing an important role in organic synthesis with a variety of application in commercial processing. It was first discovered by Ugai *et al.* in 1943, that a thiazolium salt could be an active catalyst for acyloin condensation.¹⁸⁹ To more understand this reaction, Breslow reported in detail the mechanism of the benzoin condensation, involving several steps. Among them, the nucleophilic addition of the free carbene to carbonyl compound to form the so-called “Breslow intermediate” was considered as the key intermediate for this transformation.¹⁹⁰ Until now, plenty of NHCs were developed for different targets, in which there are three commonly families of this class, including thiazolylidene, Imidazolylidene and triazolylidene (Scheme 51).



Scheme 51: Structure of some of the most common classes of NHCs

There are two major applications for carbenes. Firstly, NHCs could be used as ligands for the coordination to transition metals. After the discovery of Ruthenium carbene catalyst (Hoveyda-Grubbs II) for the olefin metathesis, thousands works were reported for designing new ligands to approach high selectivity for the *Z* or the *E*-isomer, and high enantiomeric excess (see Olefin metathesis). The second example for NHC-metal complexes was applied to palladium-catalysed cross-couplings such as Suzuki-Miyaura, Heck or Negishi reaction.¹⁹¹ One of the typical is Pd-PEPPSI-IPr, developed by Organ *et al.* that is easily prepared, highly-active

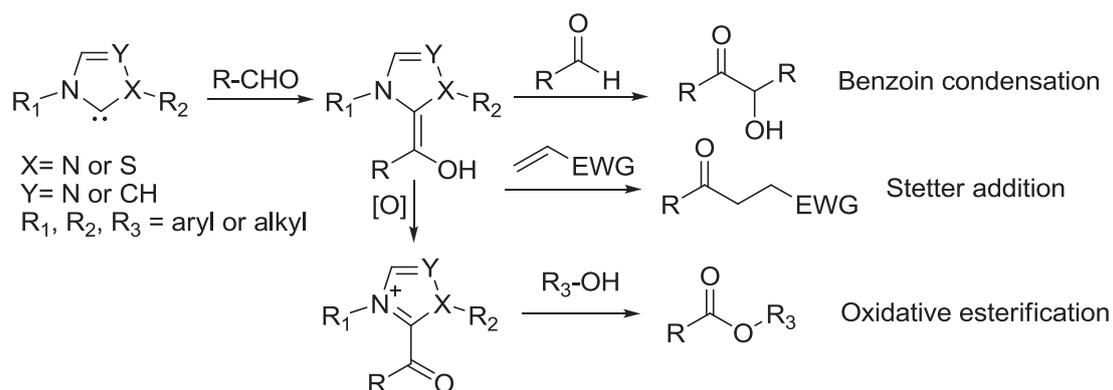
¹⁸⁹ T. Ukai, R. Tanaka, T. A. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, 63, 296–304.

¹⁹⁰ R. Breslow, *J. Am. Chem. Soc.* **1958**, 80, 3719–3726.

¹⁹¹ M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, 510, 485–496.

stabilized catalyst and commercially available for alkyl-aryl cross coupling with many applications in pharmaceuticals.¹⁹²

Secondly, the free-carbenes could be used as organocatalysts for a wide array of transformations.^{191,193} This activity was mainly based on the “umpolung” concept,¹⁹⁴ involving the attack of carbene onto a carbonyl group on the substrates to generate the so-called “Breslow intermediate”,¹⁹⁰ then this species reacts with aldehyde, Michael acceptor or ester to access the desired products (Scheme 52). In fact, there are a variety of applications related to this reactivity, but in the context of this thesis, only some of the dominant transformations that could be applied to fatty acid derivatives, will be presented.



Scheme 52: The major NHCs organocatalysts for transformation of oleochemical platforms

4.1.1 Benzoin condensation

One of the first applications of NHCs was to use these species as active catalysts for the benzoin condensation. Although this reaction was exploited since a long time notably with cyanides¹⁹⁵ then with NHCs such as thiazolium salts or imidazolium salts,¹⁹⁴ racemic mixtures of acyloin products were always observed. Initial attempt for the asymmetric benzoin condensation was described by Sheehan *et al.*, using a chiral thiazolium salt as the catalyst.¹⁹⁶ However, a low yield or a low enantiomeric excess were observed. After the use of triazolium salts, one of the most efficient NHC to access highly enantioselective transformation was reported by Connor *et al.*¹⁹⁷ In the presence of a triazolylidene precursor (4-8 mol%), the benzoin condensation of aromatic aldehydes provided more than 90% yield of α -hydroxyketones with high enantiomeric excess (>90%) (Scheme 53). A key of this catalytic

¹⁹² C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743–4748.

¹⁹³ a) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307–9387; b) J. Read de Alaniz, T. Rovis, *Synlett.* **2009**, *8*, 1189–1207; c) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000; d) D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39–92.

¹⁹⁴ D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655.

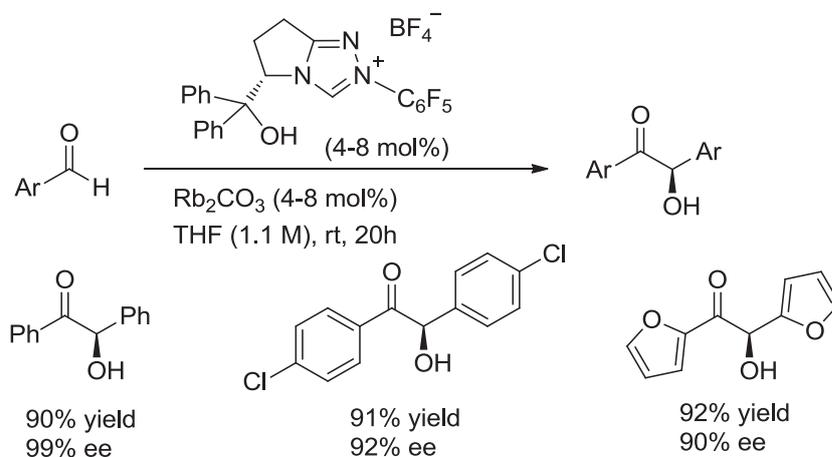
¹⁹⁵ F. Wohler and J. Liebig, *Ann. Pharm.* **1832**, *3*, 249–282.

¹⁹⁶ a) J. C. Sheehan, D. H. Hunneman, *J. Am. Chem. Soc.* **1966**, *88*, 3666–3667.; b) J. C. Sheehan, T. Hara, *J. Org. Chem.* **1974**, *39*, 1196–1199.

¹⁹⁷ L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2009**, *74*, 9214–9217.

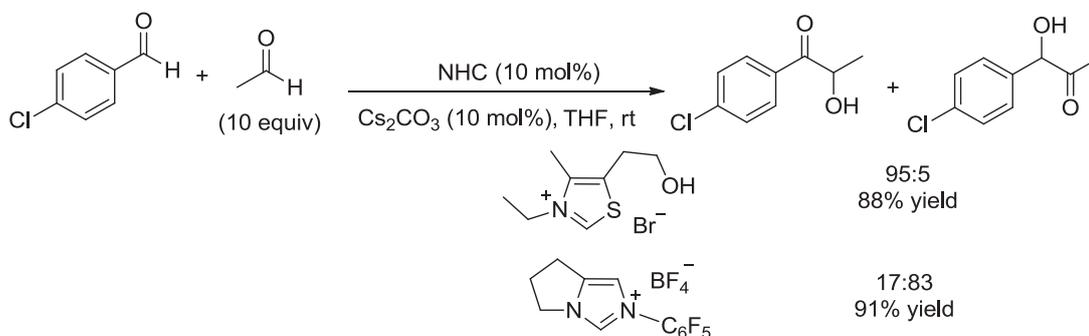
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activity was due to the presence of an OH group in the triazolylidene catalyst that helps to control the enantioselectivity.



Scheme 53: Highly enantioselective triazolium catalyst for benzoin condensation

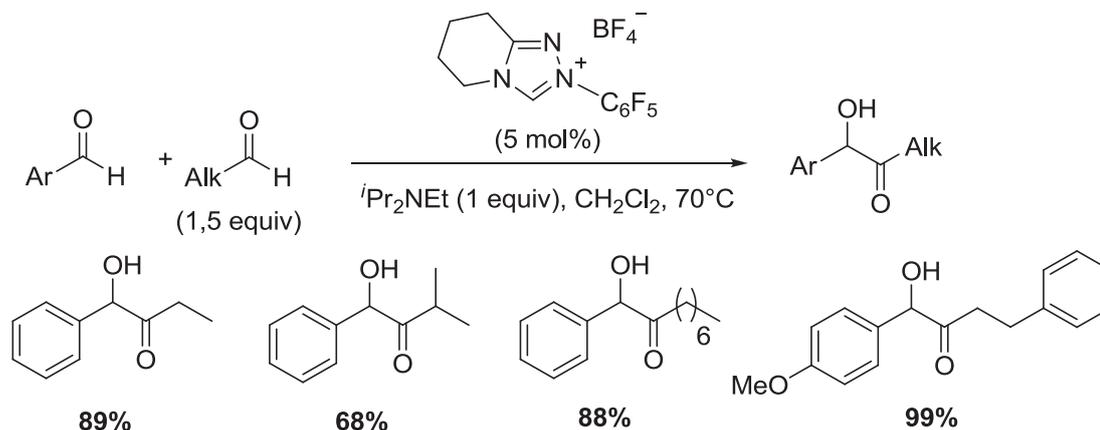
The second challenge for the benzoin condensation was the cross-benzoin condensation between aromatic aldehydes with aliphatic or aromatic aldehydes. In fact, the cross-benzoin of two aldehydes could provide a mixture of 4 products. Then, several strategies were proposed to access a good yield of cross-benzoin condensation products such as an excess of aliphatic aldehyde or selective formation of Breslow intermediate with aliphatic aldehydes. The first pathway was reported by Yang *et al.*, who described the condensation of 4-chlorobenzaldehyde with an excess of acetaldehyde (10 equiv) in the presence of thiazolium or triazolium salts (Scheme 54).¹⁹⁸ A good yield of cross-benzoin products was achieved for both catalysts. Interestingly, each catalyst could promote the formation of different regioisomers, due to the difference in electronic and steric properties. On the one hand, nucleophilic attack of thiazolium salt on aromatic aldehyde rather than acetaldehyde affords the most resonance-stabilized Breslow intermediate that reacts with acetaldehyde to release the thermodynamically stable product. On the contrary, the more sterically demanding triazolium prefers to attack the aliphatic aldehyde than aromatic one, thus promoting the formation of the second regioisomer.



Scheme 54: Cross aryl-alkyl benzoin condensation in the presence of thiazolium or triazolium catalyst

¹⁹⁸ M. Y. Jin, S. M. Kim, H. Han, D. H. Ryu, J. W. Yang, *Org. Lett.* **2011**, *13*, 880-883.

A similar strategy for cross aryl-alkyl benzoin condensation was developed by Gravel *et al.*, using a triazolium catalysts incorporating a fused morpholine or piperidine ring, that prefers to generate the Breslow intermediate with aliphatic aldehyde than aromatic aldehyde.¹⁹⁹ Instead of using a high excess of aliphatic aldehyde such as the Yang's studies, only slight excess of aliphatic aldehydes (1.5 equiv) was used and good yields from 61-99% of cross-benzoin products were obtained with a range of aliphatic aldehydes (Scheme 55).



Scheme 55: Cross-benzoin condensation between aliphatic and aromatic aldehyde

One example of application of NHC catalysis to the biomass transformation is the synthesis of 5,5'-dihydroxymethyl furoin (DHFM) from 5-hydroxymethyl furfural (5-HMF). Indeed, 5-HMF is an interesting bio-based platform that is synthesized *via* the dehydration of fructose.²⁰⁰ This compound was used as a key intermediate for the preparation of new surfactants or bio-polymers.^{201,202} The benzoin condensation of HMF in the presence of ionic liquid or triazolium salt gave DHMF as a potential monomer. This reaction required a certain amount of catalyst (1 mol%) in green solvents such as water or ethanol and provided a quantitative yield for the desired product (DHMF). Moreover, this derivative could be hydrogenated *via* hydrodeoxygenation (HDO) process at high temperature to give a mixture of premium hydrocarbon fuels (Scheme 56, route a).²⁰³ Otherwise, DHMF could be reduced or oxidized to polyol substrates which could be useful for the preparation of polyurethanes or polyesters (Scheme 56, route b and c).²⁰⁴⁻²⁰⁵

¹⁹⁹ S. M. Langdon, M. M. D. Wilde, K. Thai, M. Gravel, *J. Am. Chem. Soc.* **2014**, *136*, 7539–7542.

²⁰⁰ H. Zhao, J. E. Holladay, H. Brown, Z. C. Zhang, *Science* **2007**, *316*, 1597-1600.

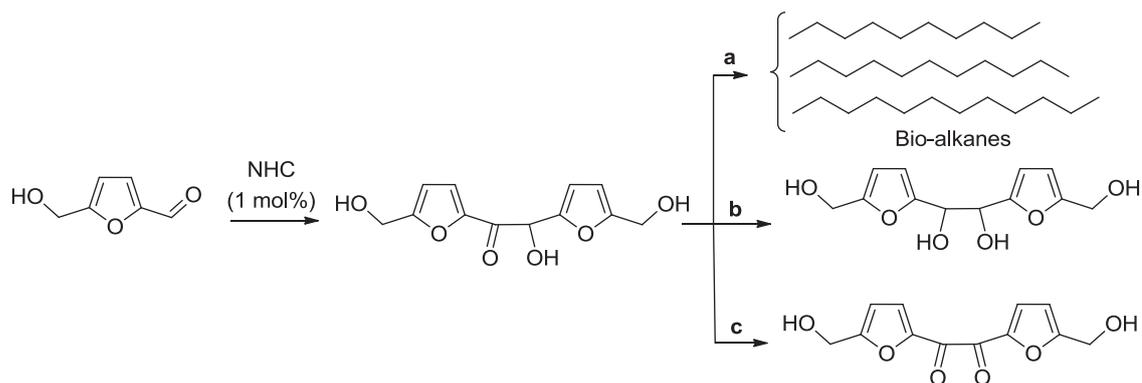
²⁰¹ K. S. Arias, M. J. Climent, A. Corma, S. Iborra, *ChemSusChem* **2014**, *7*, 210-220.

²⁰² D. Zhanga and M.-J. Dumon, *Polym. Chem.* **2018**, *9*, 743-756.

²⁰³ D. Liu and E. Y.-X. Chen, *ChemSusChem* **2013**, *6*, 2236-2239.

²⁰⁴ Z. Mou, S. K. Feng, E. Y. X. Chen, *Polym. Chem.* **2016**, *7*, 1593–1602.

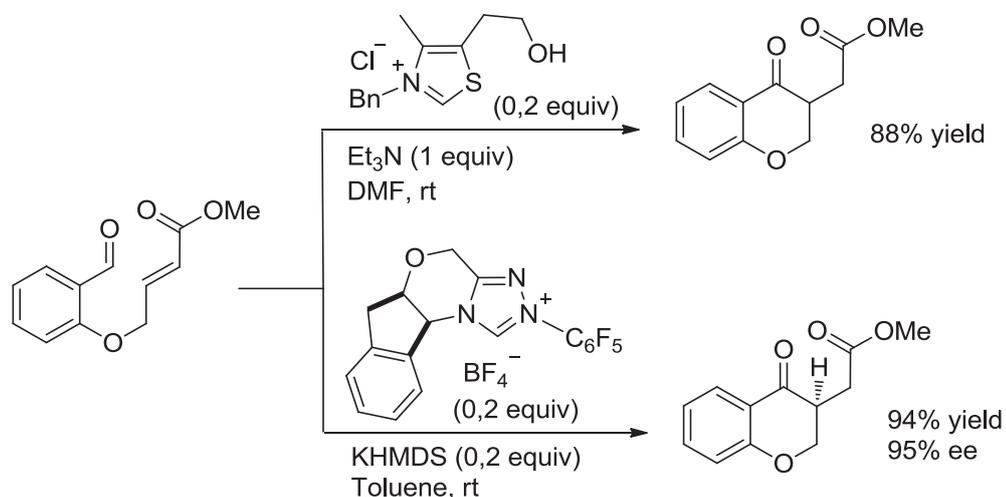
²⁰⁵ Z. Mou and E. Y.-X. Chen, *ACS Sustainable Chem. Eng.* **2016**, *4*, 7118–7129.



Scheme 56: Synthesis of bio-based platformes derived from HMF

4.1.2 Stetter reaction

The Stetter reaction, first reported in 1976, is the addition of an aldehyde onto a Michael acceptor in the presence of free carbene.²⁰⁶ In comparison with the benzoin condensation that involves a 1,2-addition, the Stetter reaction involves the attachment of an acyl anion equivalent to a Michael acceptor, leading to 1,4-dicarbonyl derivatives that make the reaction irreversible, contrary to the benzoin condensation. The first intramolecular Stetter reaction was reported by Ciganek *et al.*²⁰⁷ using a thiazolium catalyst and a good yield of cyclic product was obtained with salicylic aldehyde derivative. To obtain a high enantioselectivity, a chiral triazolium catalyst was developed by Rovis *et al.*, then an excellent yield and enantiomeric excess were achieved (Scheme 57).²⁰⁸



Scheme 57: Intramolecular Stetter reaction in the presence of thiazolium or triazolium catalyst

Intermolecular Stetter reaction is also an useful transformation in the preparation of 1,4-dicarbonyl compounds that could be converted to other interesting chemical platforms such as pyrrole moiety in pharmaceutical chemistry. The Stetter process was carried out in

²⁰⁶ H. Stetter, *Angew. Chem. Int. Ed* **1976**, *15*, 639-712.

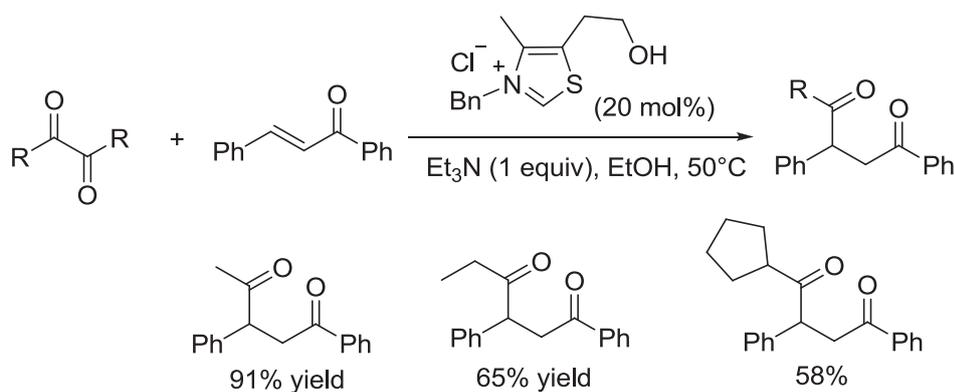
²⁰⁷ E. Ciganek, *Synthesis* **1995**, *10*, 1311-1314.

²⁰⁸ J. Read de Alaniz and T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 6284-6289.

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the presence of both aromatic and aliphatic aldehydes with a range of Michael acceptors such as vinyl phosphonates, vinyl sulfones or nitroolefin derivatives.^{209,210} It was clearly seen that Stetter reaction performed well with aromatic aldehydes. On the contrary, the Stetter process with aliphatic aldehydes gave only moderate yields. An important difference between these two families of aldehydes is based on the reactivity of α -hydroxyketone products. On the one hand, the retro-benzoin condensation occurs with aromatic substrates at room temperature, leading to an equilibrium between α -hydroxyketone and aldehydes. On the other hand, high temperatures are required to accelerate the retro-benzoin condensation of aliphatic α -hydroxyketones.²¹¹

In order to circumvent the generation of self-benzoin condensation products, symmetric vicinal diketones were used as acyl anion precursors. The work, pioneered by Massi *et al.*, then continued by Yoshida *et al.* indicated that a good yield could be achieved with short chain diketones or cyclic diketones.²¹² However, a limitation was observed with long chain diacyl substrates (Scheme 58).



Scheme 58: Stetter reaction in the presence of diketones as acyl anion precursors

The domino retrobenzoin-Stetter reaction of carbohydrates was first reported by Chi *et al.*²¹³ This consecutive reaction employs glucose as the formyl surrogate in the presence of a thiazolium catalyst under microwaves irradiation. The key step of this process involves the retrobenzoin condensation of glucose to give formaldehyde equivalents. This nucleophilic formyl group could react with chalcones to give β -formyl ketones with high yields (up to 83%).

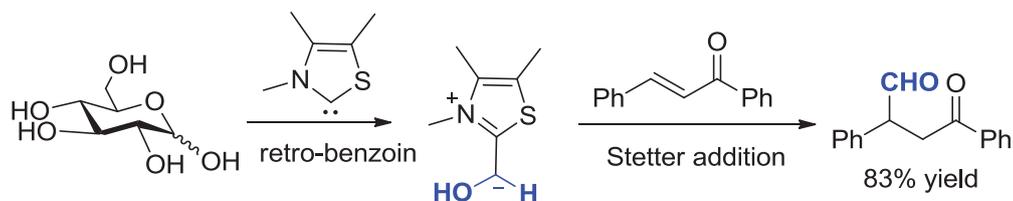
²⁰⁹ a) A. Patra, A. Bhunia, A. T. Biju, *Org. Lett.* **2014**, *16*, 4798-4801.; b) A. Bhunia, S. R. Yetra, S. S. Bhojgude, A. T. Biju, *Org. Lett.* **2012**, *14*, 2830-2833.

²¹⁰ D. A. DiRocco, E. L. Noey, K. N. Houk, T. Rovis, *Angew. Chem. Int. Ed.* **2012**, *51*, 2391-2394.

²¹¹ N. D. Vu, S. Bah, E. Deruer, N. Duguet, M. Lemaire, *Chem. Eur. J.* **2018**, *24*, 8141-8150.

²¹² a) O. Bortolini, G. Fantin, M. Fogagnolo, P. P. Giovannini, A. Massi, S. Pacifico, *Org. Biomol. Chem.* **2011**, *9*, 8437-8444.; b) K. Takaki, A. Ohno, M. Hino, T. Shitaoka, K. Komeyama, H. Yoshida, *Chem. Commun.* **2014**, *50*, 12285-12288.

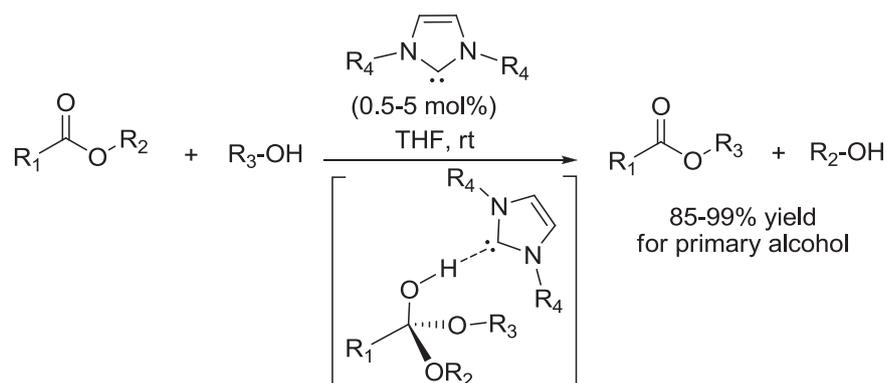
²¹³ J. Zhang, C. Xing, B. Tiwari, Y. R. Chi, *J. Am. Chem. Soc.* **2013**, *135*, 8113-8116.



Scheme 59: NHC-catalyzed domino retrobenzoin-Stetter reaction of carbohydrates

4.1.3 Transesterification

The transesterification using imidazolium catalyst was developed independently by the group of Nolan and an other group supervised by Hendrick and Waymouth. In 2002, Nolan *et al.* reported that the transesterification of methyl acetate or vinyl acetate with simple primary alcohols such as benzyl alcohol or geraniol in the presence of IMes or ICy provided good yields of the desired products (93-99% yield) (Scheme 60).²¹⁴ At the same time, Hendrick and Waymouth also described the transesterification of methyl benzoate with an excess of alcohol (20 equiv) in the presence of an imidazolydene catalyst.²¹⁵ A range of alcohols including primary, secondary and tertiary alcohols, was also investigated and the transesterification was performed well with primary alcohols. However, a slight decrease of reactivity was observed with secondary alcohols and no transesterification products were obtained with tertiary alcohols, indicating the limitation of this method. To deeper understand the mechanism of this process, a computational work by Hu *et al.* showed that the reaction was not passing through the Breslow intermediate.²¹⁶ The key of this transesterification involves the formation of imidazolydene species with the Brönsted-base, then leads to a zwitterionic intermediate. It was also shown that NHC facilitates the proton transfer from the alcohol to leaving group, without ionization of the intermediate.



Scheme 60: NHC-catalyzed transesterification of unactivated ester

4.1.4 Oxidative esterification

The oxidative esterification using carbene catalysis is also of great interest. By using external oxidants such as MnO_2 , benzoquinone or oxygen, the Breslow intermediate could be

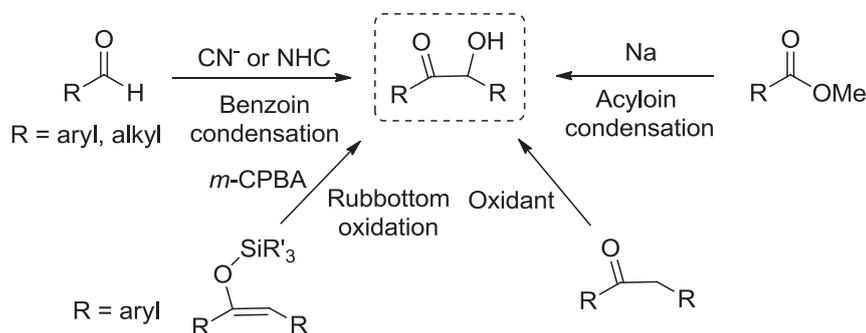
²¹⁴ G. A. Grasa, R. M. Kissling, S. P. Nolan, *Org. Lett.* **2012**, *4*, 3583-3586.

²¹⁵ G. W. Nyce, J. A. Lamboy, E. F. Connor, R. M. Waymouth, J. L. Hedrick, *Org. Lett.* **2012**, *4*, 3587-3790.

²¹⁶ C.-L. Lai, H. M. Lee, C.-H. Hu, *Tetrahedron Lett.* **2005**, *46*, 6265-6270.

1. State of art for the preparation of fatty α -hydroxyketones

Vegetable oil derivatives are key intermediates for bio-transformations of biomass. Some of them are directly converted to bio-diesel which is considered as an alternative fuel. Next to this, a lot of attempts were done to valorize this family of compounds to higher added-value such as epoxidized vegetable oils (EVOs) for plasticizers, biosourced diols for polymers, etc. Among them, α -hydroxyketone is an interesting functional group. However, the synthesis of these substrates was underexploited on fatty derivatives. Actually, there are a few routes to prepare this kind of compounds such as benzoin condensation,²¹⁸ acyloin condensation,²¹⁹⁻²²⁰ rubottom oxidation,²²¹ oxidation of ketone derivatives,²²² etc (Scheme 62).



Scheme 62: Traditional pathways for the preparation of α -hydroxyketone derivatives

However, most of these methods could not be applied to the synthesis α -hydroxyketones derived from vegetable oils. In this context, only methodologies to prepare fatty α -ketol derivatives will be presented.

1.1 Oxidation of alkene

In an early report, a method was developed by Holde and Marcusson then King using KMnO_4 “neutral” to oxidize oleic acid **1** to 9(10)-hydroxy 10(9)-oxooctadecanoic acid **2a** and **2b**. However, this method has worked in very high diluted conditions (1 g/l) with a low yield (30%).²²³⁻²²⁴ This work was also re-investigated by Swern *et al.*²²⁵ Swern found that 45% yield of a 1:1 mixture of two regioisomers **2a** and **2b** were always afforded even if the pH was controlled or not. Moreover, the best yield (70%) of α -hydroxyketones was obtained when the pH of the medium was controlled between 9.0 and 9.5 using a solution of phosphate buffer (Scheme 63).

²¹⁸ S. M. Langdon, M. M. D. Wilde, K. Thai, M. Gravel, *J. Am. Chem. Soc.* **2014**, *136*, 7359-7542.

²¹⁹ K. T. Finley, *Chem. Rev.* **1964**, *64*, 573-589.

²²⁰ J. J. Bloomfield, D. C. Owsley, C. Ainsworth, R. E. Robertson, *J. Org. Chem.* **1975**, *40*, 393-402.

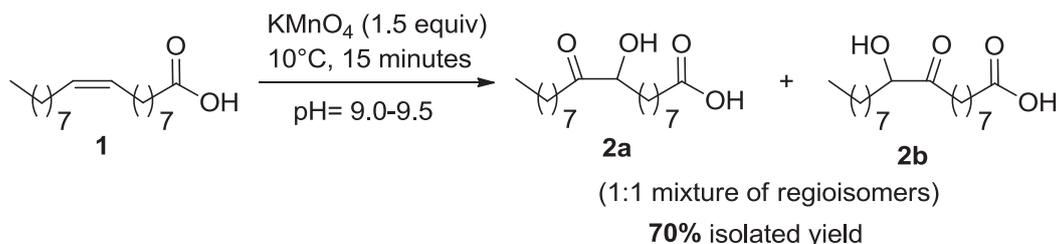
²²¹ J. Christoffers, A. Baro, T. Werner, *Adv. Synth. Catal.* **2014**, *346*, 143-151.

²²² C. Chen, X. Feng, G. Zhang, Q. Zhao, G. Huang, *Synthesis* **2008**, 3205-3208.

²²³ D. Holde and J. Marcusson, *Ber.* **1903**, *36*, 2657-2662.

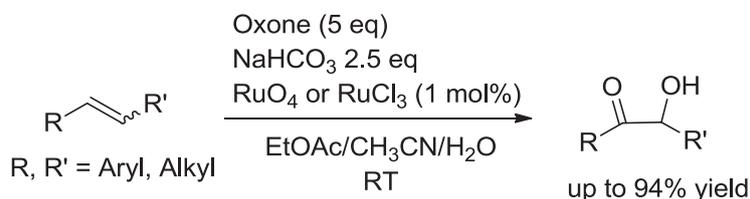
²²⁴ G. King, *J. Chem. Soc.* **1936**, 1788-1792.

²²⁵ E. Coleman, C. Ricciuti, D. Swern, *J. Am. Chem. Soc.* **1956**, *78*, 5342-5345.



Scheme 63: Oxidation of oleic acid to corresponding α -ketol using “neutral” KMnO_4

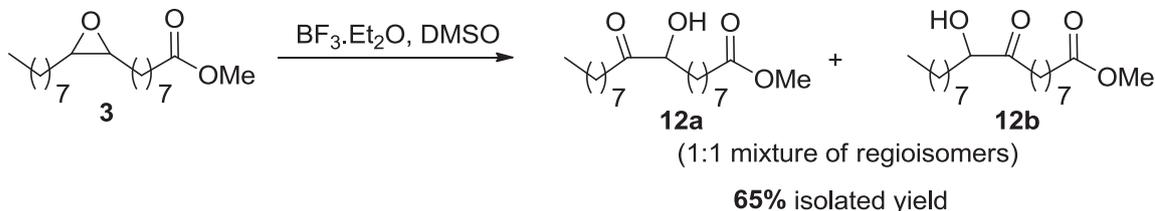
More recently, Plietker developed a mild condition for ketohydroxylation of olefin using RuO_4 as a catalyst.²²⁶⁻²²⁷ This method was performed in a mixture of solvents ($\text{EtOAc}/\text{CH}_3\text{CN}/\text{H}_2\text{O}$) at room temperature using an excess of oxone as an oxidant to give an excellent yield of α -hydroxyketone derivatives (up to 94% for aromatic substrates) (Scheme 64). However, oxone is a strong oxidant and a very exothermic agent, then it could be probably a problem to upscale the reaction. Moreover, no fatty acid derivatives has been tested by the authors.



Scheme 64: Ketohydroxylation of olefin using Ru -based catalyst

1.2 Opening of epoxide

Epoxidized fatty compounds are interesting derivatives for synthesis of α -ketol oleochemicals. A study by Brousse and Lefort showed that 65% yield of hydroxyketone derivatives **12a** and **12b** can be obtained by oxidative ring-opening of epoxidized methyl oleate **3** in the presence of a Lewis acid as $\text{BF}_3 \cdot \text{Et}_2\text{O}$, using DMSO as an oxidant (Scheme 65).²²⁸ However, this method generates dimethyl sulfide as a co-product which is madolorous and toxic gas. Recently, this work was repeated by Deruer *et al.*²²⁹ However, only 42% of the fatty ketols **12a** and **12b** was reported, indicating that this method suffers from a lack of reproductivity.



Scheme 65: Oxidative ring-opening of epoxidized fatty compounds to ketol derivatives

²²⁶ B. Plietker, *J. Org. Chem.* **2003**, 68, 7123-7125.

²²⁷ B. Plietker, *J. Org. Chem.* **2004**, 69, 8287-8296.

²²⁸ E. Brousse and D. Lefort, *C. R. Acad. Sci.* **1965**, 261(groupe 8), 1990-1991.

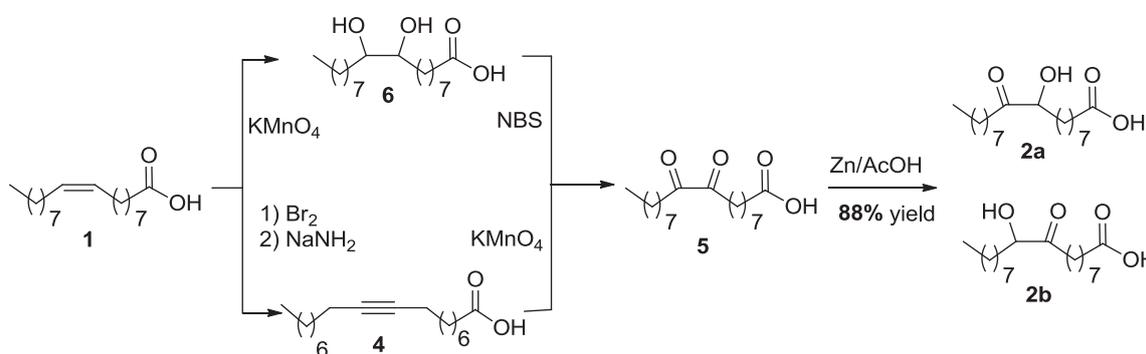
²²⁹ E. Deruer, N. Duguet, M. Lemaire, *ChemSusChem* **2015**, 8, 2481-2486.

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A similar study was reported to synthesize α -ketol fatty acids. However, a low yield was obtained, with the concomitant formation of the corresponding diols (18-30% yield) as unwanted products.²³⁰

1.3 Monoreduction of diketone:

Another strategy to access fatty α -hydroxyketones is the monoreduction of vicinal diketones.²³¹ Actually, there are two main pathways to access 1,2-diketones: 1) oxidation of vicinal diols with NBS or 2) oxidation of a fatty alkynoic acid (Scheme 66). Among two of them, route 1 is more preferable because dihydroxylated compound is easy to synthesis and circumvents with the use of toxic agents such as bromide or NaNH_2 . Then, the vicinal diketone was reduced to corresponding α -ketols **2a** and **2b** using Zinc in AcOH to obtain the desired products with a high yield (88%). However, this method suffers from the formation of a large quantity of metal waste and a lack of selectivity.



Scheme 66: Synthesis of α -ketol from vicinal diketone

1.4 Mono-oxidation of diol

There are a variety of methods to oxidize 1,2-diols to α -hydroxyketone derivatives. In an early work, Fétizon *et al.* reported that a cyclic diol substrate such as cyclohexane-1,2-diol could be converted into corresponding α -ketol using an excess of silver carbonate with a moderate yield (41%).²³² This phenomenon was explained by the formation of overoxidation products (vicinal diketones). More recently, several oxidation systems were reported to promote this reaction such as $\text{NaBrO}_3/\text{NaHSO}_3$,²³³ $\text{KBrO}_3/\text{KHSO}_4$,²³⁴ dioxirane.²³⁵ However, most of them are used in a stoichiometric amount. Besides, a few catalytic oxidation methods were developed based on RuO_4 -oxone,²³⁶ boronic acid-dibromoisocyanuric acid,²³⁷ Pd-benzoquinone.²³⁸ They usually exhibit a good selectivity for desired product. However, they generate large amount of waste and the scope is quite limited. In most cases, they gave good yields with aromatic derivatives and short linear chain substrates. However, no example was reported with fatty compounds such as the diol derived from oleic acid.

²³⁰ T. M. Santosussolb, D. Swern, *J. Org. Chem* **1975**, *40*, 2764-2769.

²³¹ W. A. Cramp, F. J. Julietti, J. F. McGhie, B. L. Rao, W. A. Ross, *J. Chem. Soc.* **1960**, 4257-4263

²³² M. Fétizon, M. Golfier, J.-M. Louis, *J. Chem. Soc. Chem. Commun.* **1969**, 1102-1102.

²³³ M. Bierenstiel, P. J. D'Hondt, M. Schlaf, *Tetrahedron* **2005**, *61*, 4911-4917.

²³⁴ J. M. William, M. Kuriyama, O. Onomura, *Tetrahedron Lett.* **2014**, *55*, 6589-6592.

²³⁵ K. Jakka, C.-G. Zhao, *Org. Lett.* **2006**, *8*, 3013-3015.

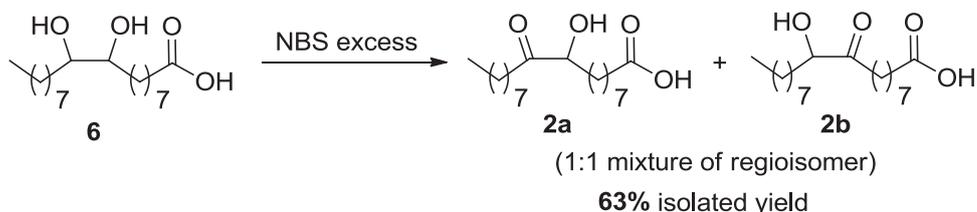
²³⁶ B. Plietker, *Org. Lett.* **2004**, *6*, 289-291.

²³⁷ J. M. William, M. Kuriyama, O. Onomura, *Adv. Synth. Catal.* **2014**, *356*, 934-940.

²³⁸ R. M. Painter, D. M. Pearson, R. M. Waymouth, *Angew. Chem. Int. Ed.* **2010**, *49*, 9456-9459.

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In the literature, there is only one paper describing the mono-oxidation of fatty substrates. The diol derived from oleic acid **6** was oxidized to the corresponding ketols **2a** and **2b** using *N*-Bromo succinimide (NBS) as an oxidant (Scheme 67).²³¹ However, the desired products were only obtained with 63% yield (Scheme 66), due to the formation of an inevitable by-product (1,2-diketone). Moreover, the reaction involving NBS is highly exothermic and the reaction generates a large amount of chemical waste, leading to a difficult purification process.



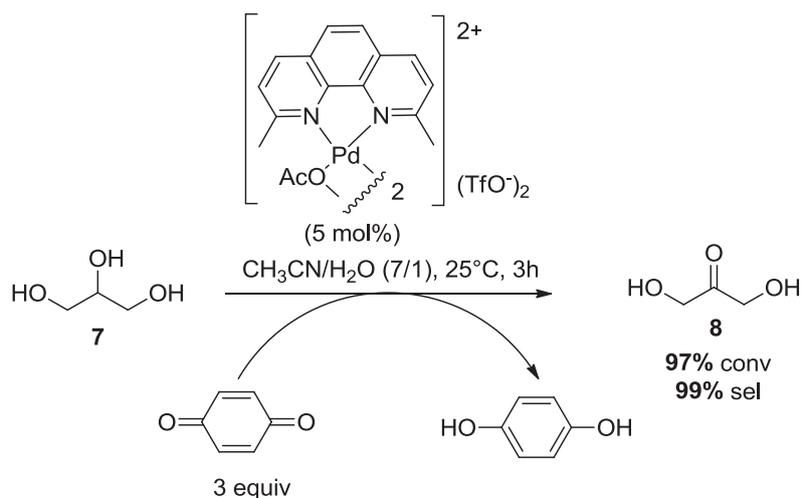
Scheme 67: Synthesis of fatty α -ketol from fatty vicinal diol

Until now, the mono-oxidation of fatty vicinal diols to corresponding ketols is quite under-investigated. In this context, the development of an efficient method to obtain this family of compounds is highly desired.

2. Mono-oxidation of vicinal diols

2.1 Waymouth's work

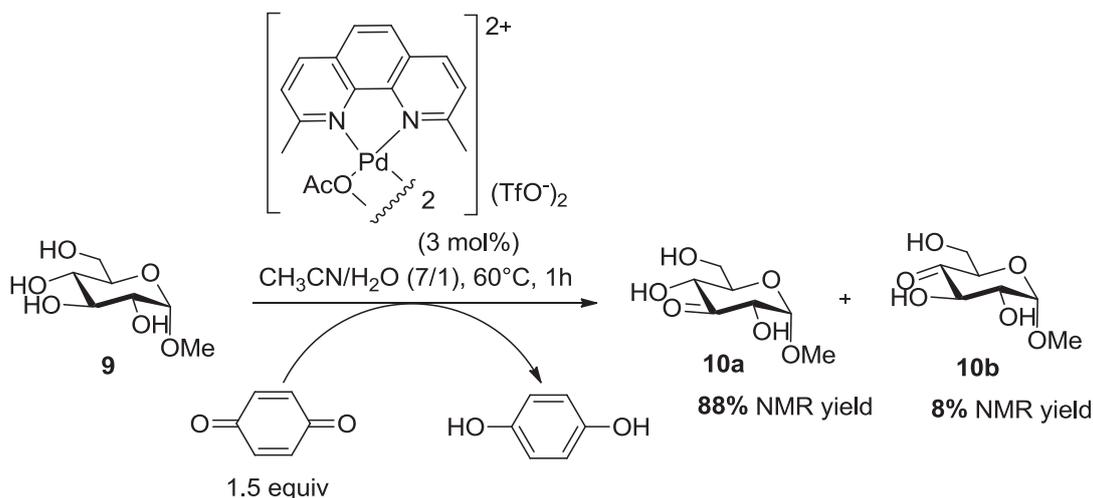
Recently, Waymouth *et al.* have reported a method for the selective oxidation of glycerol **7** to dihydroxyacetone (DHA) **8** using a complex between $\text{Pd}(\text{OAc})_2$ and neocuproine as catalyst and benzoquinone (3 equiv) as an oxidant under ambient temperature.²³⁸ This method gave a good conversion (>97%) and excellent selectivity (99%) towards the formation of DHA (Scheme 68).



Scheme 68: Selective oxidation of glycerol to dihydroxyacetone

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This strategy was also applied for unprotected carbohydrate derivatives and exhibits good results with many advantages such as a low catalyst loading and excellent conversion.²³⁹ However, the selectivity of the desired products was lower than for glycerol. This phenomenon could be explained by the presence of many secondary alcohols. The formation of 3-ketose **10a** was the major product (88%) (Scheme 69). However, the generation of 4-ketose **10b** was also formed (8%) as an inevitable co-product.



Herein, Waymouth *et al.* have developed a mild condition for selective mono-oxidation of polyols. The reaction was carried out for both carbohydrates and simple polyols and provided good yields of desired products. However, some drawbacks still exist such as the use of oxidants. On the one hand, benzoquinone could generate a large amount of hydroquinone that renders the purification process more difficult. On the other hand, the use of a greener oxidant such O₂ could lead to the formation of over-oxidation products or the oxidation of the ligand. Moreover, no example for unactivated fatty 1,2-diol was given by the authors.

2.2 Preliminary results²⁴⁰⁻²⁴¹

Inspired by Waymouth's study,²³⁸ we first attempted the selective mono-oxidation of diol **11** under their optimized conditions (5 mol% Pd-neocuproine complex, 3 equiv benzoquinone, CH₃CN or DMSO, rt). However, no α -hydroxyketone was obtained, probably due to the lack of solubility of diol **11**. Then, the reaction conditions were reinvestigated, using oxygen as a green oxidant. At the beginning, the reaction was conducted in a sealed tube, using Pd(OAc)₂-neocuproine (4 mol%), oxygen (1 bar) in MeOH at 50°C for 3 hours. Under these conditions, the conversion reached 58%, the selectivity of α -hydroxyketones **12** reached 93% and some black particles (Pd⁰) were observed (Table 2, entry 1). Realizing that the pressure of oxygen gradually decreased as the reaction progress, the reaction was next carried out in a stainless steel reactor using a constant pressure of oxygen (3

²³⁹ K. Chung, R. M. Waymouth, *ACS Catal.* **2016**, *6*, 4653–4659.

²⁴⁰ This part was done during my master internship in 2015, supervised by Dr. Estelle Metay, Dr. Nicolas Duguet and Boris Guichet.

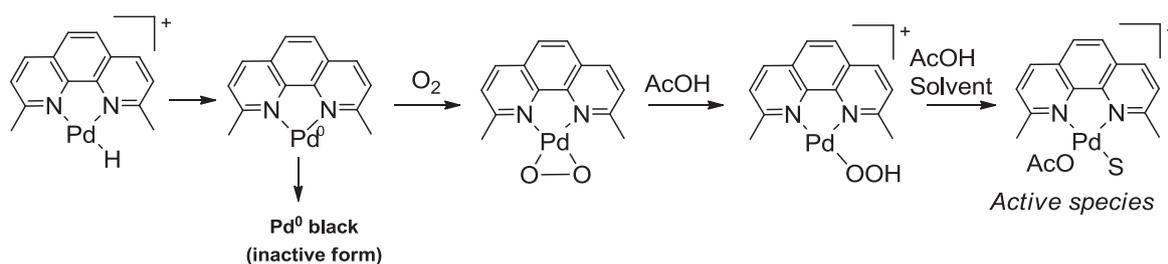
²⁴¹ N. D. Vu, B. Guichet, N. Duguet, E. Métay, M. Lemaire, *Green Chem.* **2017**, *19*, 3390–3399.

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bar). Satisfyingly, the conversion was complete after 30 minutes (Table 2, entry 2). Similar results (99% conversion, 89% selectivity) were also obtained using only 2 mol% of catalytic system. However, the reaction time was needed to extend (1.5 hours)(Table 2, entry 3). A further decrease in the catalyst loading to 1 mol% did not allow the reaction to achieve complete conversion (Table 2, entry 4), then catalyst loading of 2 mol% was selected for next investigation.

The oxidant was next probed for mono-oxidation of diol **11** under previous optimized conditions. Excellent results (95% conversion, 99% selectivity) were obtained with benzoquinone (1 equiv) (Table 2, entry 5). However, this oxidant suffers from a formation of a large quantity of chemical waste (hydroquinone). A green oxidant such as hydrogen peroxide (35% in H₂O) was also investigated under these conditions. A good result of 83% conversion and 91% selectivity was observed when H₂O₂ (1 equiv) was used (Table 2, entry 6). However, an increase of oxidant (H₂O₂, 2 equiv) did not affect the selectivity but the conversion dramatically dropped to 26%, caused by the oxidation of methyl group in neocuproine, affecting the structural integrity of the ligand and thus decreasing the rate of the reaction (Table 2, entry 7).

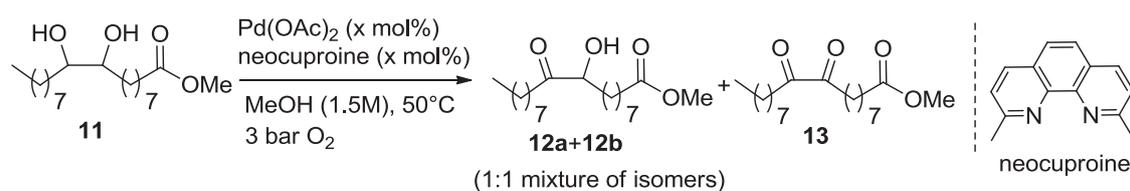
The use of basic or acidic additives was next investigated for mono-oxidation of diol **11**. A good selectivity (95%) toward the formation of α -hydroxyketone **12** was obtained in the presence of AcONa (6 mol%) (Table 2, entry 8). However, the conversion declined to 75%. On the contrary, the use of acid was rather surprising. Excellent results (95% conversion, 97% selectivity) were obtained using AcOH (6 mol%) as an additive after 1.5 hours (Table 2, entry 9). Addition of some acetic acid is beneficial to the reaction by preventing Palladium black formation and accelerating the reoxidation of Pd(0) or Pd(II) peroxy to Pd(II) acetate species that is true active species in this catalytic cycle (Scheme 70).²⁴² No better results (94% conversion, 94% selectivity) was observed in the presence of AcOH (12 mol%) but extended reaction time (3 hours) was required in the case (Table 2, entry 10). This is likely due to the addition of acetic acid hindering the initial deprotonation of diol **11**.



²⁴² a) D. R. Jenson, M. J. Schultz, J. A. Mueller, M. S. Sigman, *Angew. Chem. Int. Ed.* **2003**, *42*, 3810-3813; b) J. A. Mueller, C. P. Goller, M. S. Sigman, *J. Am. Chem. Soc.* **2004**, *126*, 9724-9734; c) L. M. Dornan, G. M. A. Clendenning, M. B. Pitak, S. J. Coles, Mark J. Muldoon, *Catal. Sci. Technol.* **2014**, *4*, 2526-2534.

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Table 2: Optimisation of mono-oxidation of diol **11** using Pd-neocuproine complex ^a



Entry	Catalyst loading (mol%)	Oxidant	Additive (mol%)	Conv. ^b (%)	Sel. 12 ^b	Sel. 13 ^b
1	4	O ₂ (1 bar)	-	58	93	1
2	4	O ₂ (3 bar)	-	99	90	10
3	2	O ₂ (3 bar)	-	99	89	8
4	1	O ₂ (3 bar)	-	67	93	2
5	2	BQ (1 equiv)	-	95	99	1
6	2	H ₂ O ₂ (2 equiv)	-	83	91	3
7	2	H ₂ O ₂ (2 equiv)	-	26	85	1
8	2	O ₂ (3 bar)	CH ₃ COONa(6)	75	95	5
9	2	O₂ (3 bar)	AcOH(6)	95	97	3
10	2	O ₂ (3 bar)	AcOH(12)	94	94	3

^areaction conditions: 20 mL sealed tube or 30 mL steel reactor, 3 mmol of **11**, Pd(OAc)₂ (x mol%), neocuproine (x mol%), MeOH (1.5M), 50°C; ^bDetermined by GC analysis.

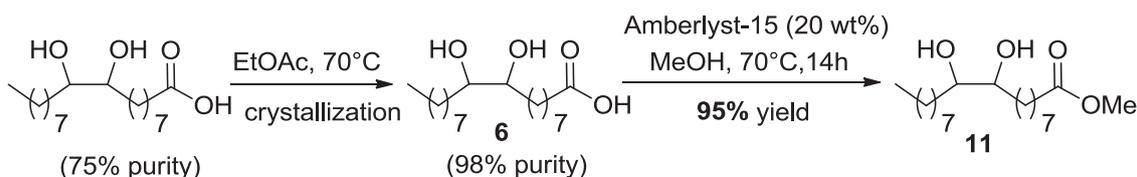
2.3 Scope for optimized conditions

We have first developed an optimized condition for the mono-oxidation of fatty diol **11** to the corresponding α -hydroxyketones **12** using catalytic system Pd-neocuproine. These conditions were next applied to biomass substrates. However, these derivatives were not commercially available and need to be prepared on the multigram scale. The biosourced fatty-1,2 diols were synthesized from cheap and available substrates such as high-oleic sunflower oil, rapeseed oil or castor oil.

2.3.1 Preparation of biosourced vicinal diols

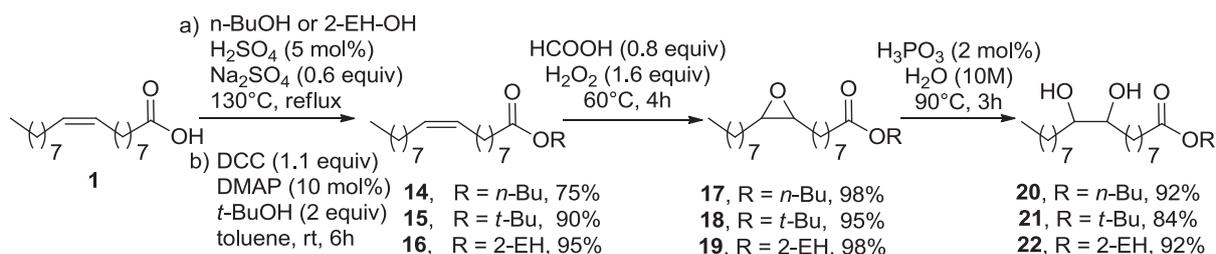
The diol **11** was prepared from the crude product (75% purity) diol oleic acid **6** supplied by Oleon. This crude product was first crystallized in ethyl acetate to obtain the high-purity (98%) fatty diol **6**. Then this derivative was esterified in excess MeOH at 70°C in the presence of Amberlyst-15 (20 wt% compared to diol **6**). After 14 hours, the reaction was complete and the desired product **11** was obtained in an excellent yield (95%) (Scheme 71).

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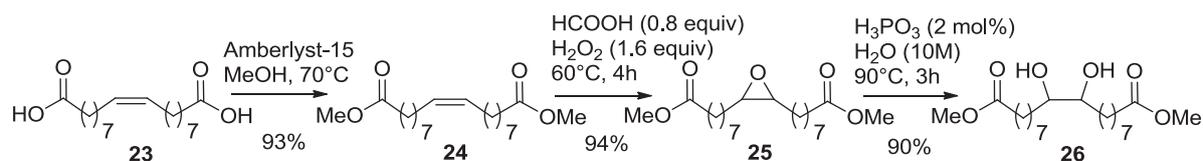
Scheme 71: General procedure for the preparation of fatty diol **11** from industrial crude products

The fatty esters **14** and **16** were prepared by esterification of oleic acid **1** with *n*-butanol or 2-ethylhexanol (in excess and solvents), using sulfuric acid as an acid catalyst and sodium sulfate as a water scavenger. These reactions were heated at 130°C during 75 minutes and provided the corresponding esters **14** and **16** in 75% and 90% yield, respectively. The *t*-butyl ester analogue could not be synthesized by this method because of the steric hindrance and the low reactivity of *tert*-butanol. Then, Mitsunobu esterification was applied in the presence of DCC and DMAP to give the desired product **15** with 90% yield. All the 3 fatty esters **14**, **15** and **16** were converted to their corresponding epoxides **17**, **18** and **19** using a reported process²⁴³ with quantitative yields (95-98%). Finally, these epoxides were converted to the diol derivatives by hydrolysis in the presence of H₃PO₃ and water. The corresponding fatty diols **20**, **21** and **22** were obtained with 92, 84 and 92% yield, respectively (Scheme 72).



Scheme 72: General procedure to access biosourced fatty diols

The preparation of two symmetrical diols **26** and **29** were also considered. These compounds could be synthesized by a similar route, starting from the self-metathesis products of methyl oleate. However, these alkene intermediates were not commercially available and Grubbs catalyst is quite expensive, then we decided to access these diols from convenient pathways. The diol diester **26** was synthesized by a similar pathway from octadecenedioic acid (O.D.A) **23** (80% purity, supplied by Oleon). Firstly, the diacid **23** was converted to the corresponding fatty diester **24** in the presence of Amberlyst-15 in the excess of MeOH. Then, the epoxidation of this derivative was conducted in a mixture of HCOOH and H₂O₂, followed by hydrolysis of fatty oxirane **25** in the presence of H₃PO₃ to give the desired fatty diol **26** with high yields (Scheme 73).

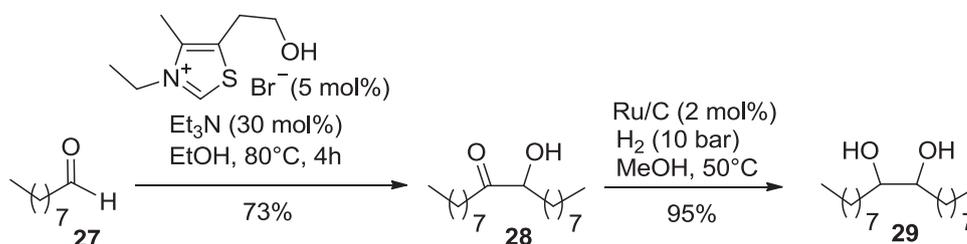


Scheme 73: The preparation of symmetrical fatty diol **26** from O.D.A

²⁴³ A. Sammaiah, K. V. Padmaja, R. B. N. Prasad, *J. Agric. Food. Chem.* **2014**, *62*, 4652-4660.

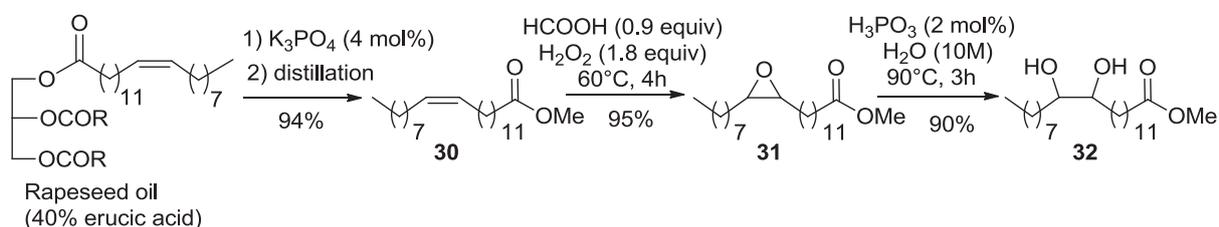
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The second symmetric diol **29** was prepared by a two-step synthesis. First, benzoin condensation of nonanal was conducted at 80°C using a thiazolium salt as a catalyst in the presence of triethyl amine²⁴⁴ and gave the corresponding α -hydroxyketone **28** with 73% yield. Then, this substrate was reduced under hydrogen pressure (10 bar) using a certain amount of Ru/C (5 wt%) to afford the desired product with 95% yield (Scheme 74).



Scheme 74: The preparation of symmetrical fatty diol **29** derived from nonanal

In order to prepare the diol **32** derived from methyl erucate that represents 40% of the composition of rapeseed oil, another strategy was applied (Scheme 75). Firstly, the methanolysis of rapeseed oil was conducted using K₃PO₄ in methanol to give a mixture of methyl fatty esters including methyl palmitate, methyl oleate, methyl linoleate and methyl erucate. Then, the more volatile oleochemicals were removed by fractional distillation under vacuum to give a residue containing more than 88% of methyl erucate **30** (94%). The epoxidation of this fatty ester was carried out in the presence of performic acid, following by ring-opening of epoxide **31** to give the desired product **32** in high yields.



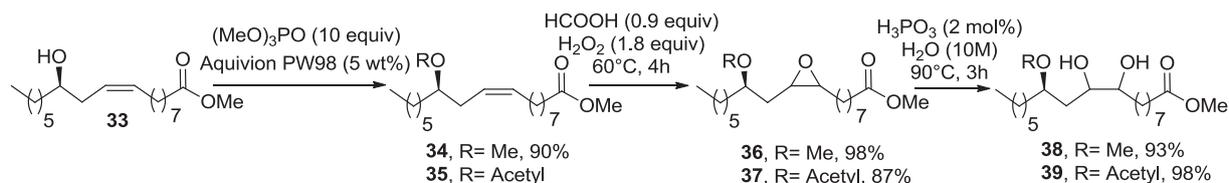
Scheme 75: Procedure for preparation of diol **32** from methyl erucate

To broaden the scope, two fatty diols **38** and **39** derived from castor oil were synthesized. On the one hand, the fatty ester **34** was prepared *via* methylation of methyl ricinoleate **33**. However, a traditional pathway using NaH/MeI did not give the desired compound. Then, a new method using trimethyl phosphate and Aquivion PW98²⁴⁵ was applied to prepare the fatty substrate **34** in a good yield (90%). On the other hand, methyl 12-O-Acyl ricinoleate (80% purity) was purchased from T.C.I chemicals then distilled under reduced pressure to give 12-O-Acyl derivative **35** with 98% purity. Both of *O*-Me and *O*-Acyl derivatives were then converted to the corresponding epoxides **36** and **37** with 98% and 87%, that were converted to fatty diols **38** and **39** in high yields (93–98%) (Scheme 76).

²⁴⁴ C. Richter, K. Schaepe, F. Glorius, B. J. Ravoo, *Chem. Commun.* **2014**, 50, 3204-3207.

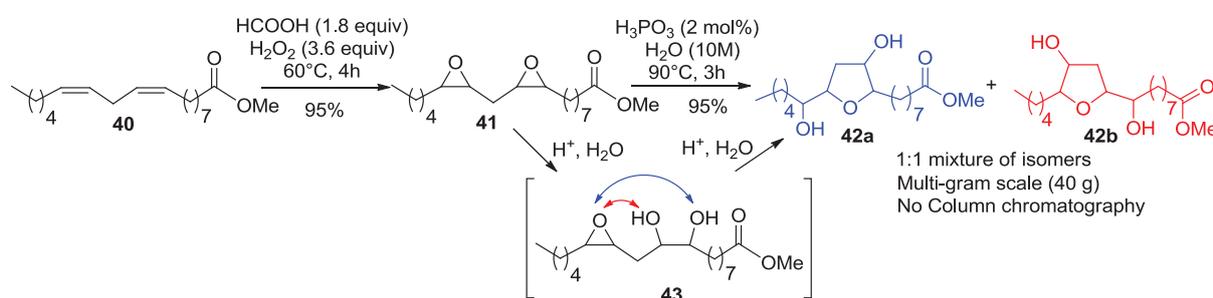
²⁴⁵ M.-C. Duclos, A. Herbinski, A.-S. Mora, E. Méta, M. Lemaire, *ChemSusChem* **2018**, 11, 547-551.

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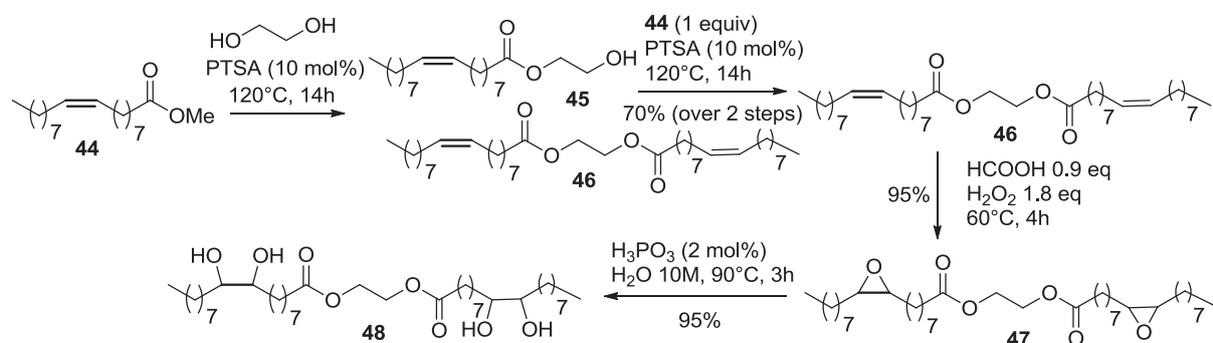
Scheme 76: Procedure for preparation of fatty diols derived from castor oil

The tetraol derived from methyl linoleate was next synthesized. The epoxidation of methyl linoleate **40** (95% purity) was carried out using performic acid to give diepoxide methyl linoleate **41** in excellent yield (95%). Then, the hydrolysis of oxirane substrate was conducted at 90°C in the presence of H_3PO_3 (2 mol%). After 3 hours, the quantitative conversion was observed but no tetraol product was reported, due to the formation of cyclic tetrahydrofuran derivatives **42a** and **42b** via intramolecular cyclisation of intermediate **43** (Scheme 77).



Scheme 77: The preparation of cyclic THF derivatives from methyl linoleate

To further increase the scope, a bis-diol was synthesized from methyl oleate and ethylene glycol. Firstly, the transesterification of methyl oleate **44** was conducted in excess of ethylene glycol at 120°C , catalyzed by *para*-toluenesulfonic acid (PTSA) to give a mixture of glycol oleate **45** (75%) and dioleate glycol **46** (20%).²⁴⁶ Then, an equivalent of methyl oleate was added in this mixture and the crude was heated at 120°C in acidic condition (PTSA, 10 mol%) to accelerate the second transesterification. After 14 hours, the conversion was complete and the glycol dioleate **46** was isolated through column chromatography with an overall yield of 70%. This fatty substrate was epoxidized by $\text{HCOOH}/\text{H}_2\text{O}_2$ to give the bis-epoxide **47**, that was converted to the bis-diol **48** in a high yield (95%) (Scheme 78)

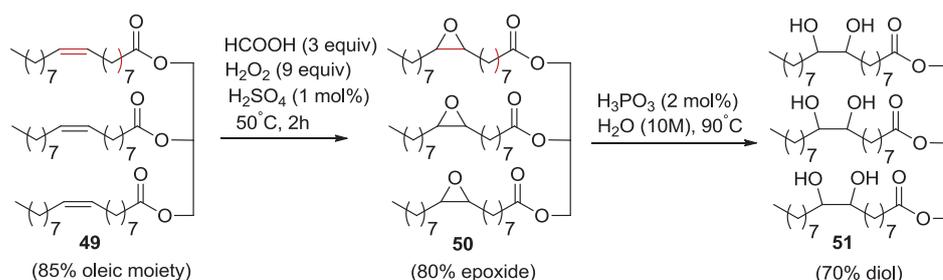


Scheme 78: Preparation of bis-diol from ethylene glycol dioleate

²⁴⁶ M. Desroches, S. Caillol, R. Auvergne, B. Boutevin, *Eur. J. Lipid Sci. Technol.* **2012**, *114*, 84–91.

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Finally, to investigate the activity of the catalytic system with raw renewable materials, a tris-diol **51** derived from high-oleic sunflower oil was synthesized. First of all, the sunflower oil containing more than 85% oleic moiety **49** was epoxidized using catalytic system of HCOOH/H₂O₂/H₂SO₄. This reaction was performed with a good conversion and selectivity to give epoxidized sunflower oil **50** (80% epoxide functionality). The rest of the mixture contains the saturated fatty derivatives and some of monoketones. Then, this intermediate was converted to vegetable oil derivatives **51** containing more than 70% of tris-diol (Scheme 79).



Scheme 79: Preparation of tris-diol derived from high-oleic sunflower oil

In conclusion, we have developed robust conditions for the synthesis of fatty diols. Even if this reaction involves a two-step synthesis but this procedure is simple, using the common and cheap catalyst as well as easy to upscale. Moreover, this reaction condition was applied to form 12 vegetable oil derivatives with 69-95% yields.

2.3.2 The scope for the mono-oxidation of 1,2-diols to α -ketols

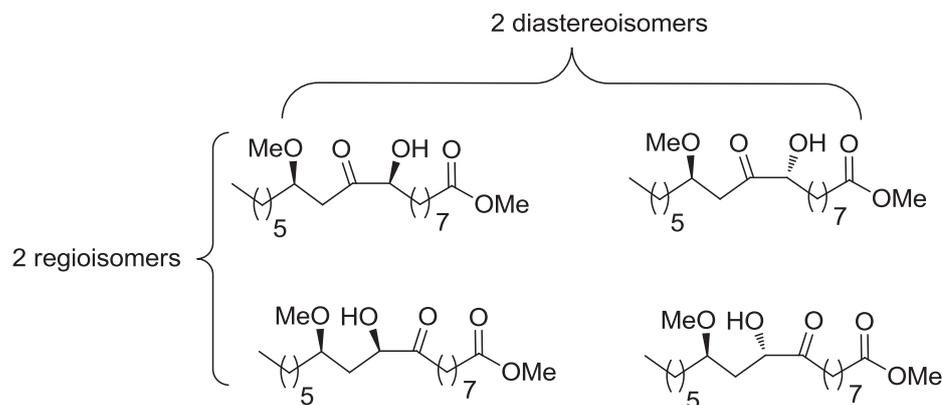
The scope for the mono-oxidation of fatty vicinal diols was initially conducted with diol **11**. The reaction was performed in an autoclave at 50°C with 2 mol% of Pd(OAc)₂ and neocuproine in the presence of AcOH (6 mol%) in the continuous pressure of oxygen (3 bar). After 1.5 hours, the conversion was nearly complete (95%) and an excellent selectivity was also obtained (Ketol/Diketone = 97/3). The desired α -hydroxyketone **12** was isolated with 80% after column chromatography (Table 3, entry 1). Then, this condition was applied to diols **20** and **21** derived from *n*-butyl and *t*-butyl oleate. Treatment of diol **20** under optimized condition gave α -hydroxyketone **52** with an excellent selectivity (95%) between ketol and diketone products, and the product **52** was isolated with 75% isolated yield (Table 3, entry 2). A similar result was observed with diol **21**. A full conversion was obtained and fatty α -ketol **53** was isolated in 78% yield (Table 3, entry 3). Then, diol **22** was successfully converted and a good yield (78%) of corresponding α -hydroxyketone **54** was achieved (Table 3, entry 4).

Two symmetrical diols **29** and **26** were next catalytically oxidized under optimized conditions. The quantitative conversion was observed with diol **29** and the corresponding α -ketol **28** was isolated with 84% yield (Table 3, entry 5). On the contrary, the conversion of diol **26** only reached 75% after 1.5 hours although 92% selectivity of desired product was provided and the desired product **55** was obtained with 61% yield (Table 3, entry 6). For the conversion of diol **32** originated

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from rapeseed oil, a full conversion was observed and 72% of α -hydroxyketone **56** was afforded (Table 3, entry 7).

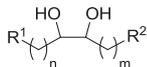
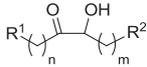
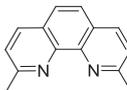
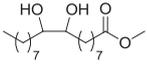
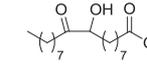
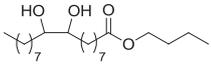
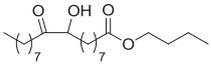
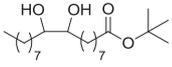
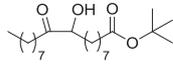
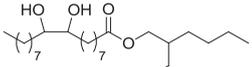
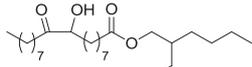
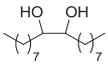
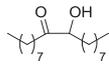
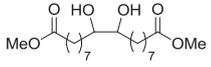
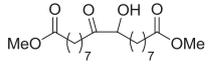
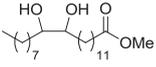
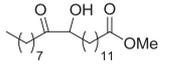
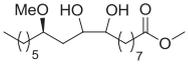
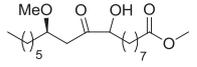
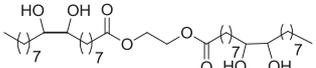
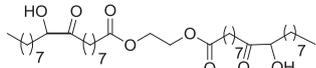
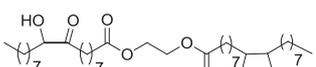
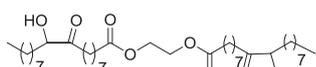
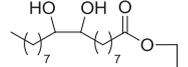
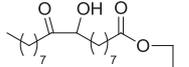
Another biosourced diol **38** which was derived from methyl ricinoleate, was also investigated. Under optimized conditions, 70% of fatty ketol **57** was isolated as a mixture of 4 isomers with a ratio of = 25:18:21:36 (Table 3, entry 8) (Scheme 80).



Then, our catalytic system was tested with challenging substrates such as **48**, **59** and **51**. For oleochemical diol **48**, un-complete conversion was reported when only 2 mol% of the catalyst was used. A mixture of products was detected after isolating each fraction by column chromatography, including bis-diol, diol-ketol, bis-ketol, ketol-diketone and bis-diketone. Then, the monooxidation of **48** was conducted in the presence of Pd-neocuproine (3 mol%) to get a better result. However, only 20% of bis-ketol was isolated and ketol-diol **59** was separated as a major product. Finally, the reaction was carried out in the presence of Pd-neocuproine (4 mol%). A complete conversion was observed after 2.5 hours and 50% of bis-ketol **58** was achieved (Table 3, entry 9). This phenomenon could be explained by the low solubility of bis-diol **48** in MeOH even at 50°C. In order to compare the reactivity of two functional groups, the compound **59** was evaluated in the adjusted condition. After 2.5 hours, 85% conversion was observed and 75% of ketol functionality was identified by NMR analysis. However, only 42% yield of the desired bis-ketol was isolated after purification (Table 3, entry 10). Finally, this catalytic system was employed for high-oleic sunflower oil derivative **51** containing at least 70% diol. The catalytic amount was calculated based on the percentage of diol detected by $^1\text{H-NMR}$. This fatty diol was fully converted and 90% of selectivity of ketol **60** was observed by $^1\text{H-NMR}$ (Table 3, entry 11). It proved that this catalytic system is stable, versatile and applicable to oleochemical derivatives including raw renewable substrates such as sunflower oil.

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Table 3: Scope for catalytic oxidation of fatty vicinal diol to corresponding α -hydroxyketone derivatives^[a]

		O_2 (3 bar) Pd(OAc) ₂ (2 mol%) neocuproine (2 mol%) AcOH (6 mol%) MeOH, 50°C, 1.5 h						
					 (1:1 mixture of isomers)	 neocuproine		
Entry	1,2-Diol	Conv. ^b (%)	Yield ^c (%)	Alpha-hydroxyketone	Isolated Yield ^c (%)	Selectivity ^b (%)		
1		11	95		12	80	97 (3% DK)	
2		20	80		52	75	95 (5% DK)	
3		21	99		53	78	80 (14% DK)	
4		22	99		54	78	80 (17% DK)	
5		29	99		28	84	90 (9% DK)	
6		26	75		55	61	92 (no DK)	
7		32	99		56	72	74 (12% DK)	
8		38	99		57	70	75 (12% DK)	
9 ^d		48	99		58	50	66 (34% DK-Ketol)	
10 ^d		59	85		58	42	75 (25% DK)	
11 ^d		51	99		60	-	90 (10% DK)	

^a Reaction conditions: 30-mL stainless steel reactor, 12 mmol of 1,2-diol, Pd(OAc)₂ (2 mol%), neocuproine (2 mol%), AcOH (6 mol%), O₂ (3 bar), MeOH (8 mL), 50°C, 1.5 hour. ^b Conversion and selectivity were determined by ¹H NMR. ^c Isolated yield after purification by column chromatography; d 4 %mol of catalyst was used; DK = 1,2-diketone

2.3 Conclusion

Herein, we first developed a mild method for mono-oxidation of biosourced fatty diols to approach α -hydroxyketones with several advantages such as high conversion and selectivity, low catalyst loading, using a green oxidant and cheap solvent (O₂ and MeOH) as well as feasibility to upscale. However, the price of catalyst was still expensive and the recyclability of homogenous catalyst was also a great challenge. Then, there was a demand for finding a complementary methodology using a heterogenous catalyst which could be recycled.

3. Dehydrogenation of vicinal diols

3.1 Dehydrogenation process

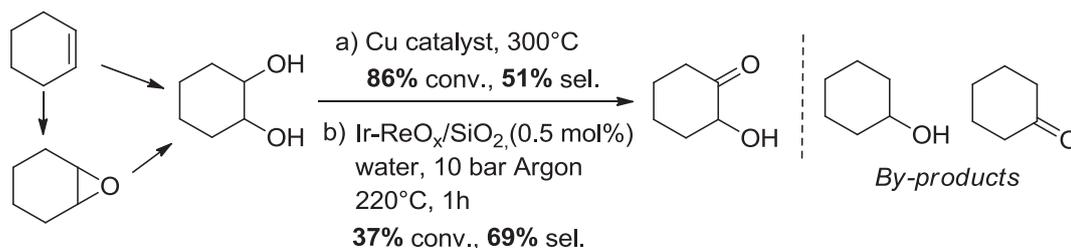
The dehydrogenation is an important reaction in organic synthesis involving the removal of hydrogen. It could be applied to convert alkane or saturated derivatives in nature to olefin derivatives which are more useful and valuable for chemical process. One of the typical example is the dehydrogenation of ethyl benzene to styrene, that is a precursor for synthesis of polystyrene, using iron oxide as a catalyst.²⁴⁷ However, this process is highly endothermic. Then, it works at high temperature (often more than 200°C) and suffers from a lack of selectivity between competitive reactions such hydrogenation, dehydration and C-C cleavage.

An α -hydroxyketone derivative could be obtained from the corresponding diol which could be easily accessed *via* ring-opening of epoxide or dihydroxylation of olefin, by a dehydrogenation process. However, this kind of reaction is quite underexploited. Until now, there have been a few reports to synthesize an α -ketol from a vicinal diol. In an early report, Molnar and Bartok have developed a method using copper as a catalyst at 300°C for the preparation of 2-hydroxy cyclohexanone.²⁴⁸ However, only 86% conversion and 51% selectivity were obtained (Scheme 81, condition a). Later, Tomishige *et al.* found that the same transformation could be done using Ir-ReO_x/SiO₂ catalyst under milder conditions (220°C, 10 bar Argon, in water).²⁴⁹ However, only 37% conversion and 69% selectivity were achieved (Scheme 81, condition b), caused by consecutive reactions to form a lot of unwanted products such as cyclohexanone and cyclohexanol.

²⁴⁷ D. H. James, W. M. Castor, *Ullmann's Encyclopedia of Industrial Chemistry*, DOI: 10.1002/14356007.a25_329.pub2

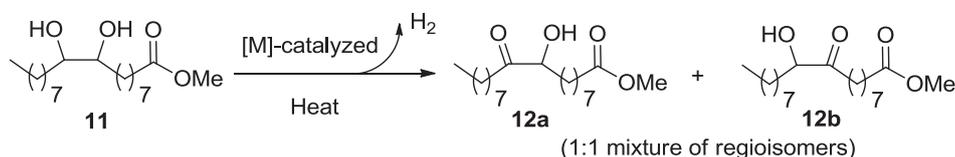
²⁴⁸ A. Molnar, M. Bartok, *React. Kinet. Catal. Lett.* **1976**, *4*, 315-321.

²⁴⁹ H. Sato, M. Tamura, Y. Nakagawa, K. Tomishige, *Chem. Lett.* **2014**, *43*, 334–336.



Scheme 81: Preparation of 2-hydroxy cyclohexanone from cyclohexane 1,2-diol

In this context, we would like to develop a methodology to synthesize fatty α -ketols from vicinal biosourced diols by dehydrogenation using a metal-based heterogeneous catalyst under solvent-free conditions without any hydrogen scavenger (Scheme 82). Methyl 9,10-dihydroxyoctadecanoate **11** was chosen as a model substrate because of its availability and typical characteristic of oleochemical compounds.

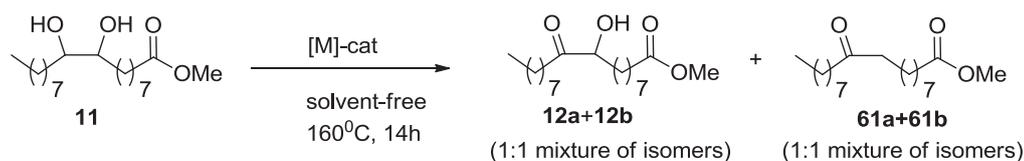


Scheme 82: Dehydrogenation of diol **11**

3.2 Nature of the dehydrogenation catalyst

First, a series of commercially available heterogeneous catalysts was investigated under solvent-free conditions. The reaction was performed at 160°C in a sealed tube under an argon atmosphere (Table 4). Using Palladium-based catalyst, no conversion was observed whatever the nature of the support (SiO₂, Al₂O₃ or BaSO₄) (Table 4, entries 1-3). A similar trend was also obtained with platinum supported on silica (Table 4, entry 4). However, the results with Ruthenium catalyst were quite promising. Ruthenium on charcoal gave 20% conversion and 35% selectivity while 45% conversion and 29% selectivity were achieved with ruthenium on alumina (Table 4, entries 5-6). Furthermore, when ruthenium hydroxide on alumina, mainly developed by Mizuno,²⁵⁰ was used, the conversion reached 50% with 60% selectivity (Table 4, entry 7). It could be explained by a better coordination of the ruthenium cation (in Mizuno's catalyst) and the fatty diol. Moreover, increase the catalyst loading of Mizuno catalyst to 5 mol% gained a slightly of conversion (62%) with the same selectivity (64%) of desired products (Table 4, entry 8). Finally, the blank experiment with only alumina gave the poor result (Table 4, entry 9), confirming the crucial role of ruthenium even if there have been disparities between different supports. This screening of heterogeneous catalyst showed that ruthenium-based catalysts are the best candidates for investigation this kind of transformation. Consequently, only ruthenium-based catalysts were used for further investigation.

²⁵⁰ N. Mizuno, K. Yamaguchi, *Catal. Today* **2008**, 132, 18-26.

Table 4: Screening of heterogeneous catalysts under solvent-free conditions


Entry	Catalyst	Loading (mol%)	Conv. (%)	Sel. 12 (%)
1	5%w-Pd/SiO ₂	2.5	0	-
2	5%w-Pd/Al ₂ O ₃	2.5	0	-
3	10%w-Pd/BaSO ₄	2.5	0	-
4	5%w-Pt/SiO ₂	2.5	0	-
5	5%w-Ru/C	2.5	20	35
6	5%w-Ru/Al ₂ O ₃	2.5	45	29
7	5%w-Ru(OH) _x /Al ₂ O ₃	2.5	50	60
8	10%w-Ru(OH) _x /Al ₂ O ₃	5	62	64
9	Al ₂ O ₃	5	0	-

Reaction condition: 20 mL sealed tube, argon atmosphere, 3 mmol of **11**.

3.3 Dehydrogenation using heterogeneous ruthenium-based catalysts

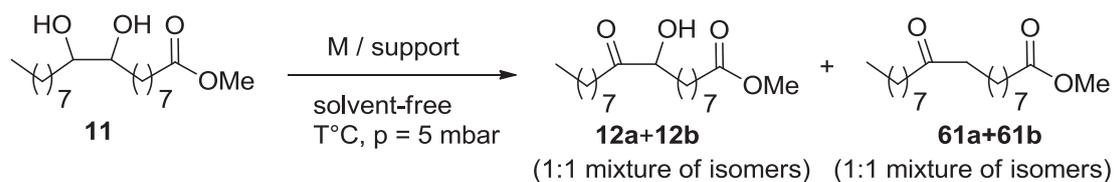
At the beginning of our investigation, the reaction was carried out in a sealed tube for the selection of the best catalysts for dehydrogenation (Table 4). However, the maximum conversion was only 62% due to the equilibrium between dehydrogenation and hydrogenation in the presence of ruthenium catalyst. To favor the dehydrogenation process, some strategies could be applied, such as using some hydrogen scavengers. However, when 1-octene, 4-vinyl anisole or 1,2-divinyl benzene were used, the results were not improved, due to the partial polymerization of vinyl derivatives or isomerization of terminal alkene at high temperature, that are less prone to be reduced, thus limiting the trap of H₂.

Another strategy is the liberation of hydrogen under reduced pressure which is better than using hydrogen scavengers especially in the view of atom economy (Table 5). First, the reaction was carried out in a schlenk tube connecting with an evaporator (for controlling the pressure). Then, the diol **11** was heated at $170^{\circ}C$ in the presence of Ru(OH)_x/Al₂O₃ (5 mol%) under vacuum pressure (5 mbar). Satisfyingly, 78% conversion and 90% selectivity of the desired product were achieved after 8 hours (Table 5, entry 1). In that case, monoketone derivatives **61a** and **61b**

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were formed as by-products by dehydration. Increasing the temperature to 180°C, the conversion improved to 91%, but on the opposite side, the selectivity declined to 75% by the formation of dehydration and C-C cleavage by-products (Table 5, entry 2). Another factor that was investigated is the loading of heterogenized catalyst. The reaction gave 83% conversion and 84% selectivity in the presence of 10 mol% of Ru(OH)_x/Al₂O₃ at 170°C (Table 5, entry 3). A similar result was obtained with 10 mol% catalyst at 180°C for 6 hours (89% conv, 83% sel) (Table 5, entry 4). Furthermore, Ru/Al₂O₃ was used under the typical conditions. At 170°C, 70% conversion and 99% selectivity were recorded in the presence of 5 mol% catalyst after 8 hours (Table 5, entry 5). A better performance was achieved with ruthenium on charcoal (80% conv, 93% sel) (Table 5, entry 6). However, during all these experiments, the mass balance remained at only 90%. This phenomenon could be explained by generation of volatile C-C cleavage products that were removed under vacuum. To circumvent this issue, the pressure was controlled at 100 mbar. When the reaction was repeated, the same results were obtained but with only a 3% mass loss, which is acceptable for this kind of reaction at high temperature using a heterogeneous catalyst. Then, the dehydrogenation reaction of diol **11** was re-investigated under this pressure.

Table 5: Dehydrogenation of diol **11** under vacuum ($p=5$ mbar)



Entry	Catalyst	Loading (mol%)	Conditions	Conv. ^b (%)	Sel. 12 ^c (%)	Mass balance (%)
1	10%w-Ru(OH) _x /Al ₂ O ₃	5	170°C, 8 h	78	90	92
2	10%w-Ru(OH) _x /Al ₂ O ₃	5	180°C, 8 h	91	75	90
3	10%w-Ru(OH) _x /Al ₂ O ₃	10	170°C, 10 h	83	84	90
4	10%w-Ru(OH) _x /Al ₂ O ₃	10	180°C, 6 h	89	83	90
5	5%w-Ru/Al ₂ O ₃	5	170°C, 8 h	70	99	90
6	5%w-Ru/C	5	170°C, 8 h	80	93	90

^a Reaction conditions: 30-mL Schlenk flask fitted with a condenser, 12 mmol of **11**. ^{b,c} Determined by GC.

To deeper understand the dehydrogenation process, the kinetics of the reaction was next studied under standard conditions (Figure 5). Diol **11** and Ru/Al₂O₃ (5 mol%) were introduced into a schlenk tube and the reaction was carried out at 175°C and at 100 mbar vacuum pressure. After 11 hours, the reaction provided 79% conversion and 70% GC yield of desired product **12** (Figure

5, blue and red curves). Interestingly, almost no conversion was observed after 4 hours. However, the conversion was dramatically risen to 70% between 4 and 6 hours. It seems that the reaction requires some time to activate the catalyst. For this reason, commercially-available ruthenium on alumina was activated under atmospheric hydrogen at 170°C for 1 hour. Surprisingly, 70% conversion and 62% GC yield of products **12** were observed after only 6 hours. Two types of Ru/C with different specific area were next applied to this strategy. The result was even better with activated 5 wt%-Ru/C ($S= 500\text{m}^2/\text{g}$). 93% of conversion and 82% GC yield of **12** were achieved after 4 hours. Furthermore, the dehydrogenation with activated 5%w-Ru/C (Escat 4401, $S= 900\text{ m}^2/\text{g}$) represented 90% conversion and 79% GC yield after 2 hours. Extending the time to 3 hours led to a complete conversion (97%) but the selectivity declined rapidly to 75%, mainly caused by the generation of undesired ketone **13** (21%). Finally, activated 5 wt%-Ru/C ($S= 500\text{m}^2/\text{g}$) was selected for scope of dehydrogenation of fatty diol derivatives.

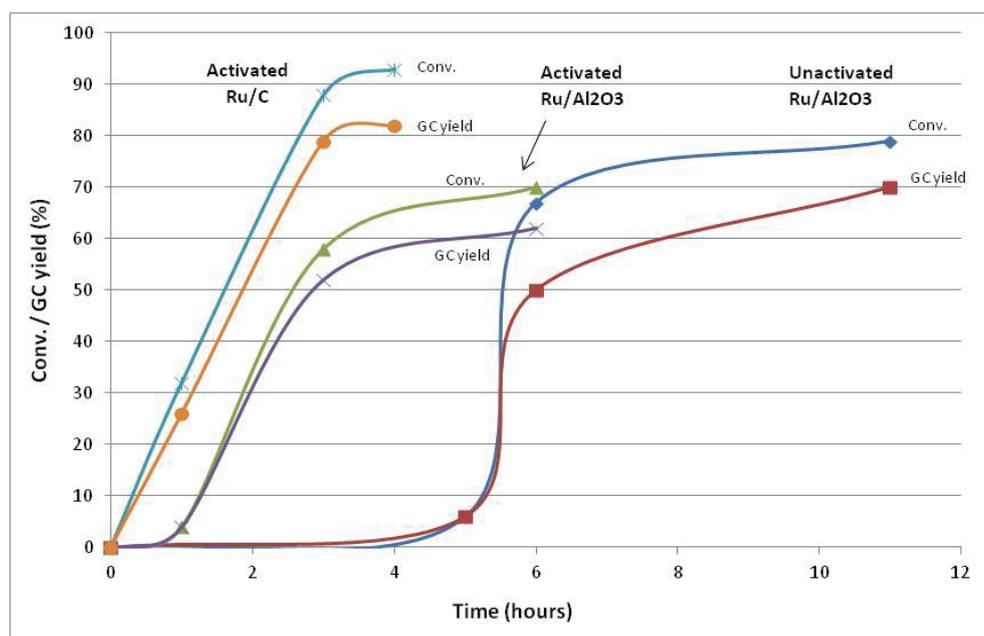
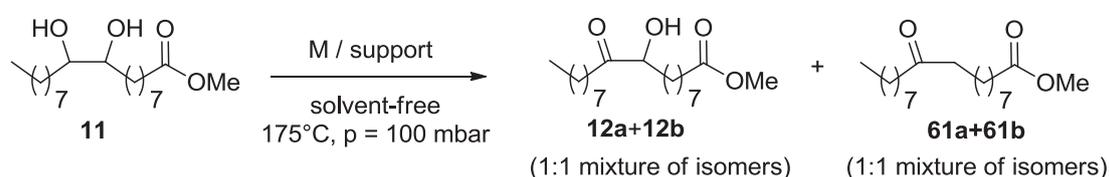


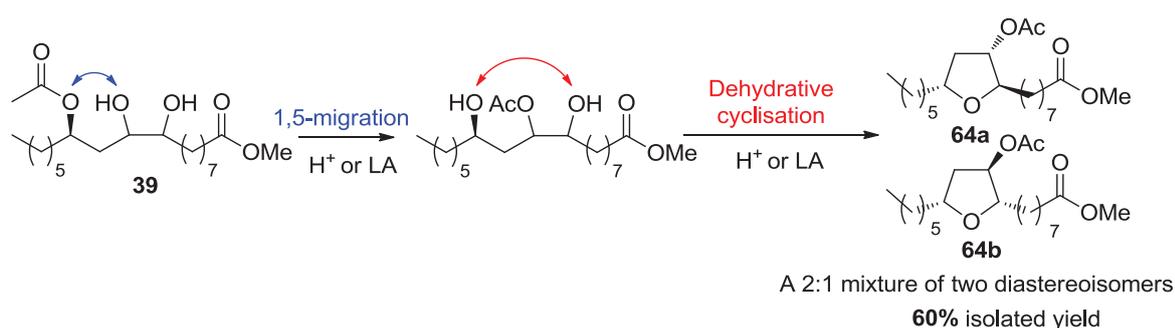
Figure 5: Dehydrogenation of diol **11** with unactivated and activated catalysts

3.4 Scope for dehydrogenation of fatty biosourced diols

The scope for the dehydrogenation of fatty diols was investigated under optimized conditions in the presence of activated Ru/C (5 mol%) at 175°C (neat, vacuum pressure = 100 mbar, 3 hours) (Table 6). The diol **11** derived from methyl oleate provided 91% conversion and 87% selectivity of corresponding α -ketol (Table 6, entry 1). After purification on column chromatography, 67% of the desired compound **12** was achieved. Diols with longer chain such as butyl and 2-ethyl hexyl

esters **20** and **22** were also examined and gave good conversions (71-75%) and good selectivities (89-92%) (Table 6, entries 2-3). Then, diol tert-butyl ester **21** was next investigated under optimized conditions. In the presence of activated Ru/C, a quantitative conversion of **21** was observed but no desired product was detected by $^1\text{H-NMR}$ (Table 6, entry 4). This phenomenon could be explained by the acidity of charcoal support. According to Park's study,²⁵¹ tert-butyl ester could be easily cleaved under microwave-irradiation in the presence of SiO_2 at 120°C . That is the reason why degradation of diol **21** occurs at high temperature (175°C) in the presence of acidic supported such as charcoal, to release of 1-butene and a mixture of un-wanted products **62a** and **62b**. To avoid the de-tert-butylation, activated $\text{Ru/Al}_2\text{O}_3$ was used and a lower conversion (40%) was observed but the selectivity of the desired product **63** still remained at 88% (Table 6, entry 5).

The protocol was subjected to symmetrical diols **25** and **26**, which were derived from the self-metathesis product of methyl oleate. Excellent conversions (93-94%) and good selectivity (85-81%) were achieved (Table 6, entries 6-7). Diol **32** originated from rapeseed oil was also probed for dehydrogenation reaction. After 3 hours, the reaction gave 85% conversion and 81% selectivity of the corresponding α -ketol **56** (Table 6, entry 8). To broaden our scope, diol **39** from methyl ricinoleate was next investigated. Although quantitative conversion was observed, no desired product was obtained but cyclic THF derivatives **64a** and **64b** were isolated with 60% yield as a 2:1 mixture of two diastereoisomers (Table 6, entry 9). In fact, a 1,5-migration of acetyl group was accelerated in diol **39** in the presence of acidic support such as charcoal, then this intermediate could be converted to THF derivatives *via* dehydrative intramolecular cyclisation (Scheme 83). A similar compound (with free OH) was recently reported by Werner *et al.* when attempting to synthesize a cyclic carbonate from methyl ricinoleate,²⁵² then supporting our hypothesis.



Scheme 83: The formation of THF derivatives from dehydrogenation of diol **39**

Finally, to evaluate the robust catalytic system, tris-diol **51** derived from sunflower oil was investigated under dehydrogenation conditions. After 6 hours, 50% conversion and 84% selectivity were observed for the corresponding α -ketol **60**, confirming that this method could be applied to renewable raw materials such as triglyceride derivatives.

²⁵¹ D. H. Park, J. H. Park, *Bull. Korean Chem. Soc.* **2009**, 30, 230–232.

²⁵² H. Büttner, C. Grimmer, J. Steinbauer, T. Werner, *ACS Sustainable Chem. Eng.* **2016**, 4, 4805-4814.

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Table 6: Scope for dehydrogenation of vicinal biosourced diols to corresponding ketol derivatives^[a]

Entry	Diol	Conv. ^b (%)	α -hydroxyketone	GC Yield ^b (%)	Sel. ^b (%)		
1		11	91		12	79 (67)	87
2		20	75		52	69 (65)	92
3		22	71		54	63 (56)	89
4		21	99		-	-	-
5 ^c		21	40		63	35 (28)	88
6		29	93		28	79 (74)	85
7		26	94		55	76 (57)	81
8		32	85		56	69 (46)	81
9		39	99		(60)	-	-
10 ^{d,e}		51	50		60	42 (nr)	84

^a Reaction conditions: 20-mL Schlenk flask, Ru/C was activated under atmospheric hydrogen pressure for 1 h at 175°C, 3 mmol of diol.

^b Determined by GC. ^c Activated Ru/Al₂O₃ was used. ^d Conversion and yield were determined by ¹H-NMR. ^e t = 6 hours.

3.5 Recycling of heterogeneous catalyst Ru/C

The recycling of heterogeneous Ru/C catalyst was investigated with model substrate **11**. First, the Ru/C catalyst was activated under hydrogen atmosphere at 175°C for 1h. Then, the catalyst and diol **11** were introduced into a schlenk tube and heated at 175°C. The reaction was carried out under a vacuum pressure of 100 mbar for 3 hours. After the first run, 90% conversion and 88% selectivity of desired products **12** were achieved. This data is quite close from those previously reported (Table 6, entry 1), confirming the reproducibility of the method. After the reaction, the catalyst was filtered, washed (EtOAc) and dried at 120°C under vacuum. This catalyst was also re-activated under hydrogen pressure at 175°C for 1 hour before re-using for a next run.

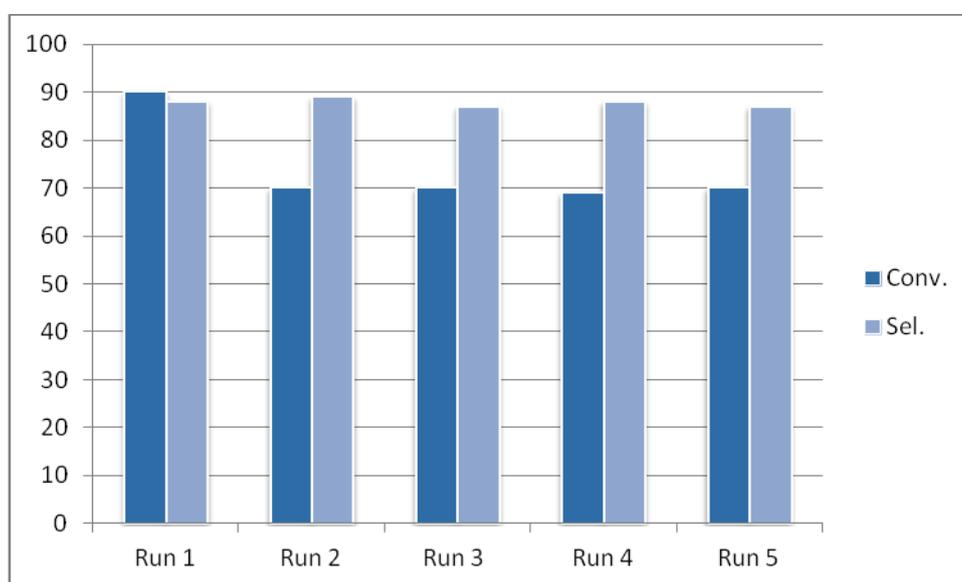


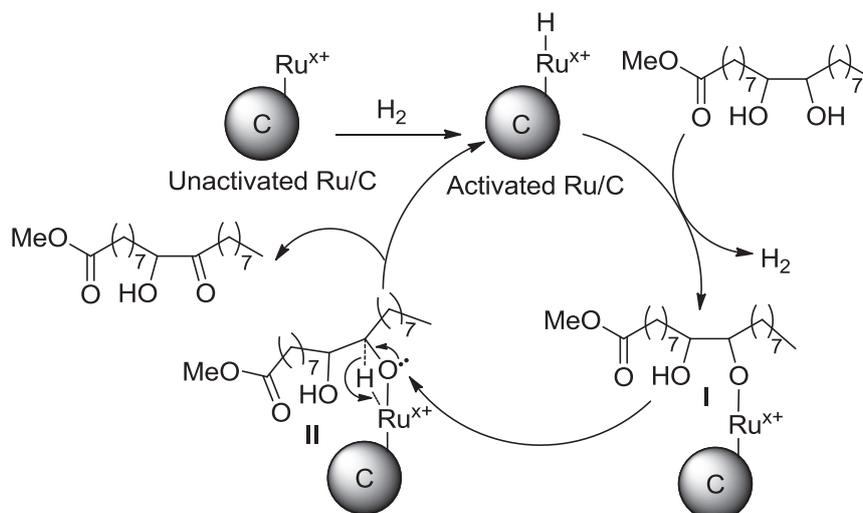
Figure 6: Recycling of heterogeneous catalyst Ru/C

In a second run, the conversion declined to 70% but selectivity remained at 88% under the same condition. Another test was done without re-activation of the catalyst. In that case, only 60% conversion was observed, showing that, it is important to re-activate the catalyst before each run. The recovered catalyst was reused for 4 consecutive cycles and the results showed that the conversion and selectivity remained at 70% and 90%, respectively. The loss of conversion between first run and second run may be caused by leaching of Ru species. However, it seems unlikely because the filtrate did not show any activity. Another explanation could be the change of the oxidation state of Ru/C during the dehydrogenation process. According to Vlachos's study,²⁵³ the oxidation state of Ru/C would change toward the loss of Ru⁴⁺ species during hydrogenation or dehydrogenation process, which might benefit to the formation of ruthenium

²⁵³ J. Jae, W. Zheng, A. M. Karim, W. Guo, R. F. Lobo, D. G. Vlachos, *ChemCatChem* **2014**, *6*, 848-856.

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hydride. In fact, the mechanism of the dehydrogenation involves two steps: ruthenium alcoholate formation and hydride elimination (Scheme 84).



Scheme 84: Proposed mechanism for dehydrogenation of diol **11** using activated Ru/C

Among two of them, hydride elimination is the rate-limiting step.²⁵⁴ To confirm the crucial role of Ru^{x+} for the dehydrogenation process, a commercially-available Ru/C was completely reduced in continuous flow of hydrogen at 300°C for 10 hours and the resulting catalyst was also activated in a schlenk tube before investigating under optimized conditions. However, only 70% conversion and 89% selectivity were obtained. To fully understand the activation/deactivation of this catalyst, a deeper study will be necessary.

4. Conclusion

We have developed two methods for the preparation of α -hydroxyketone derivatives from fatty diols. The homogeneous pathway with $\text{Pd}(\text{OAc})_2$ and neocuproine displayed a lot of advantages such as a low catalyst loading, green oxidant and solvent, low temperature as well as excellent conversion (95%) and selectivity (97%) after a short reaction time. However, the recycling of homogeneous catalyst is also great challenge and the deactivation led to a decrease the catalyst life-time. On the contrary, activated Ru/C was the best candidate for the dehydrogenation process. High conversion (91%) and good selectivity (88%) was achieved when the reaction was carried out at 175°C ($p = 100$ mbar) for 3 hours in the presence of activated Ru/C (5 mol%). Moreover, it could be reused for 5 cycles with a constant selectivity. Both these two methods were applied for a variety of fatty substrates to synthesize a range of fatty α -hydroxyketones which could be cleaved to aldehydes, acids or further functionalized.

²⁵⁴ Y. Kim, S. Ahn, J. Y. Hwang, D.-H. Ko, K.-Y. Kwon, *Catalyst* **2017**, 7, 7, DOI: 10.3390/catal7010007.

1. Retro-benzoin condensation: State of the art

Benzoin condensation is a well-known reaction for C-C formation in organic synthesis.¹⁹⁴ It was used for the preparation of (chiral) α -hydroxyketone derivatives which could be converted to heterocyclic compounds or other key intermediates for applications in pharmaceuticals or polymer industry. However, the reverse reaction that is the cleavage of α -hydroxyketones to the corresponding aldehydes, namely retro-benzoin condensation, is underexploited. As can be seen from figure 7, the number of reports related to retro-benzoin condensation is very limited in comparison with the high amount of studies about benzoin condensation.²⁵⁵

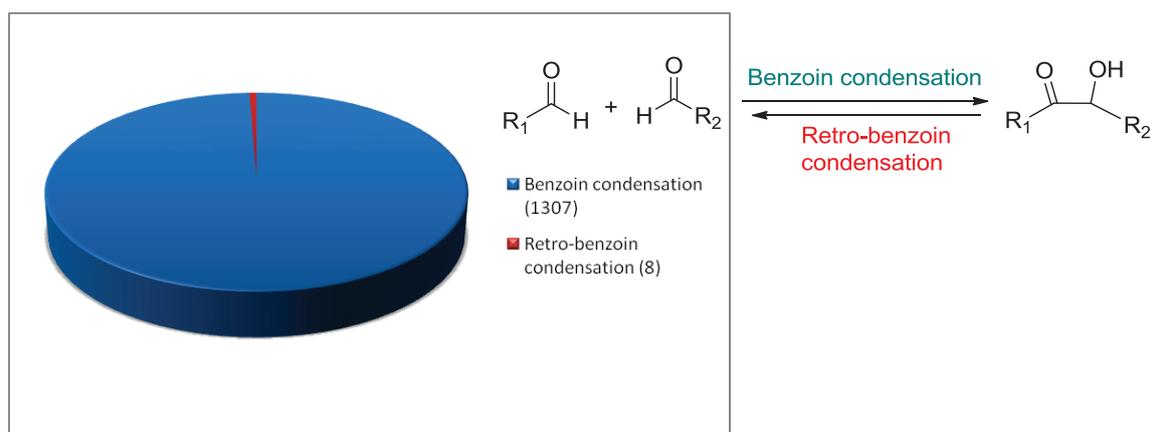


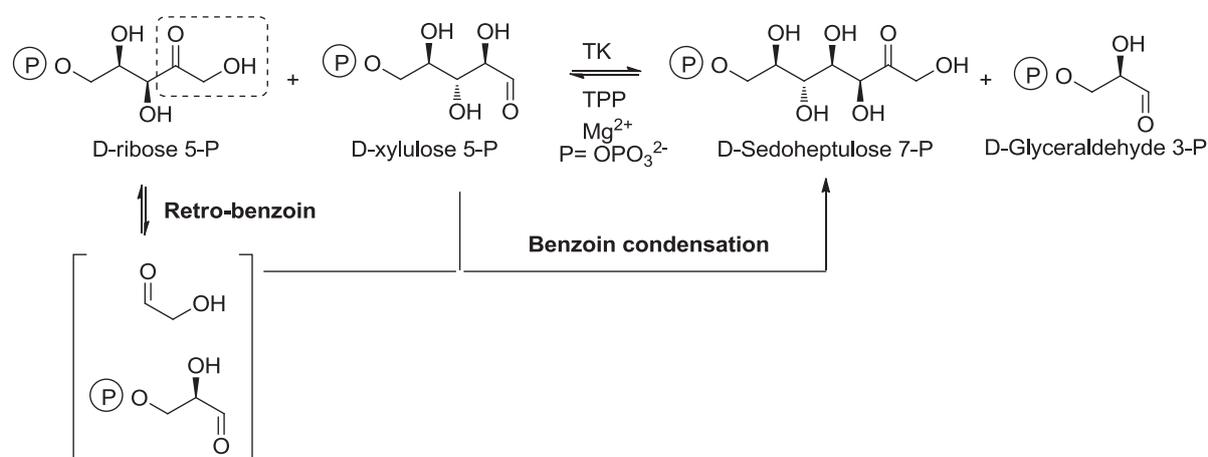
Figure 7: Comparison of the number of articles between benzoin and retro-benzoin condensation

Actually, few studies have been reported about the retro-benzoin condensation which could be seen as a bio-inspired approach. Enzymatic routes are one of the interesting pathways for bio-transformation. They bring a lot of advantages such as high reactivity, ambient temperature and water as a green solvent. However, some drawbacks might limit the application of these catalysts. For instance, the loss or reduction of activity of the catalytic system could be observed. Moreover, the disadvantages of enzymatic system should be considered such as substrate-dependence, not working at high temperature (often less than 80°C) and high cost of the process. However, enzymatic catalysis plays a crucial role in the transformation of biomass because it is closely associated with the biosynthetic or the biodegradation pathways of these renewable materials. Furthermore, a reaction catalyzed by enzymatic system is usually very specific. In some cases, it is not easy to obtain this kind of transformation by using a traditional chemical reaction. “Benzoin metathesis” of D-ribose and D-xylulose catalyzed by transketolase (TK) is one of the typical examples (Scheme 85). Actually, TK is a member of the thiamine pyrophosphate-dependent enzyme family that is related to the metabolism of carbohydrates. In the presence of TK, D-ribose was selectively cleaved at C3-position through retro-benzoin condensation to release D-glyceraldehyde and glycolaldehyde, then this C2-ketol moiety was combined with D-xylulose to generate D-sedoheptulose (C7) *via* benzoin

²⁵⁵ Scifinder® April 16th 2018, duplicates were removed for each search.

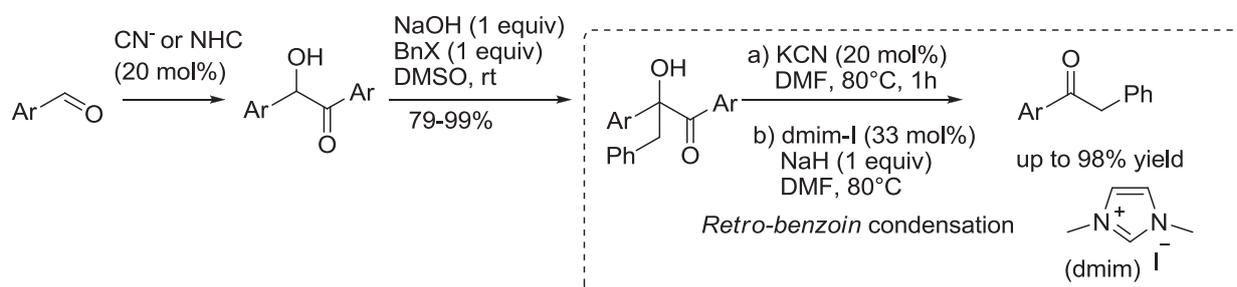
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condensation.²⁵⁶ However, the efficiency of synthetic strategy is limited, due to the reversibility of the process. But more importantly, the retro-benzoin condensation could occur in the presence of Transketolase.



Scheme 85 : Transketolase catalysed reaction in vivo using D-ribose as ketol donor

From a chemical point of view, Miyashita *et al.* were the first pioneers to apply the retro-benzoin condensation strategy to the synthesis of aromatic ketones from α -substituted benzoin (Scheme 86).²⁵⁷ Indeed, the starting materials were prepared through a two-step synthesis: benzoin condensation, then followed by nucleophilic substitution of alkyl or aryl halide in the presence of a strong base. The retro-benzoin condensation was catalysed by cyanides (CN⁻) or imidazolium salts (NHCs) to give the desired aromatic ketones with excellent yields (up to 98% for CN⁻ and 87% for NHCs). This phenomenon was explained by the formation of stable ketones, not recombining with the aromatic aldehydes generated thus shifting the equilibrium. Furthermore, other NHC precursors could be used for this transformation. For example, in the presence of 3,4,5-trimethyl thiazol-3-ium iodide, a similar result (90% yield) was observed. However, this method has a low atom-economy for the desired product and is limited to unactivated derivatives.



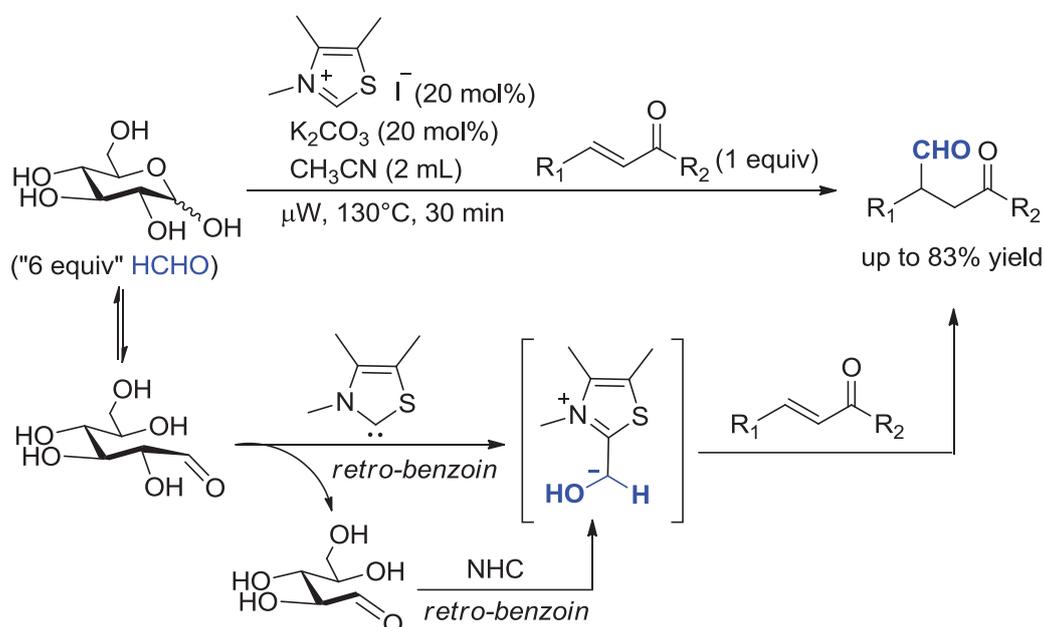
Scheme 86: Retro-benzoin condensation to preparation of aromatic ketone

²⁵⁶ N. J. Turner, *Curr. Opin. Biotechnol.* **2000**, *11*, 527-531.

²⁵⁷ a) A. Miyashita, Y. Suzuki, Y. Okumura, T. Higashino, *Chem. Pharm. Bull.* **1996**, *44*, 252-254; b) A. Miyashita, Y. Suzuki, Y. Okumura, K. Iwamoto, T. Higashino, *Chem. Pharm. Bull.* **1998**, *46*, 6-11; c) Y. Suzuki, Y. Takemura, K. Iwamoto, T. Higashino, A. Miyashita, *Chem. Pharm. Bull.* **1998**, *46*, 199-206.

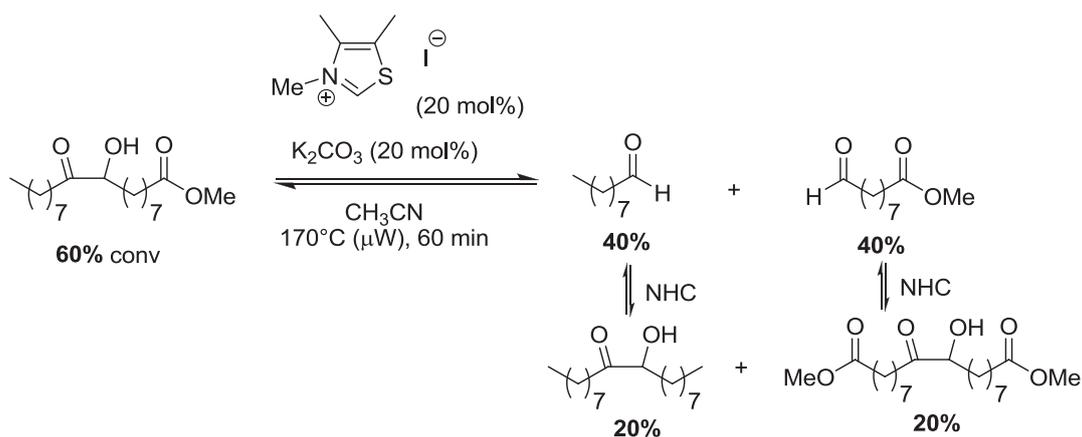
CHAPTER III: CLEAVAGE OF α -HYDROXYKETONES TO ALDEHYDES

Recently, Chi *et al.* have developed an efficient catalytic system for domino retro-benzoin and Stetter reaction using a thiazolium salt (Scheme 87).²¹³ Under microwave irradiation, glucose or other carbohydrates could react with chalcones to give β -formyl ketones in high yields, up to 83%. Actually, the key step of this transformation is the *retro-benzoin* condensation of hexose. Actually, glucose is in an equilibrium between its cyclic acetal and its acyclic aldehyde forms. The first step of this domino reaction involves the *retro-benzoin* condensation of acyclic aldehyde in the presence of thiazolylidene to release a C5-pentose and acyl thiazolium intermediate. This one-carbon nucleophilic species was trapped by a strong Michael acceptor such as chalcone to give β -formyl ketones, thus favoring the equilibrium due to irreversible character of the Stetter reaction. Moreover, the pentose could undergo further iterative NHC-catalytic cycle to generate the acyl thiazolium intermediate and other smaller carbohydrates. However, free aldehydes could not be obtained through the use of these two methods.



Scheme 87: Thiazolium salt catalyzed cascade *retro-benzoin*/Stetter reaction to β -formylketones

More recently, Duguet and Lemaire developed a method for the non-oxidative cleavage of α -hydroxyketones derived from vegetable oils to fatty aldehydes (Scheme 88).²²⁹ By investigation of a series of azolium salts (imidazolium, thiazolium and triazolium), the authors showed that the *retro-benzoin* condensation was best performed in the presence of thiazolium salts. Under microwave irradiation, the *retro-benzoin* condensation of α -hydroxyketone using catalyst 3,4,5-trimethyl thiazolium iodide (20 mol%), K₂CO₃ (20 mol%) gave 60% conversion and 40% of the desired aldehydes, with the formation of 20% of the self-benzoin condensation products.



Scheme 88: Retro-benzoin condensation of fatty α -hydroxyketone catalyzed by thiazolium salt

2. Retro-benzoin of α -hydroxyketones under microwave irradiation²⁵⁸

Based on our initial results, the retro-benzoin condensation of α -hydroxyketone **12** was investigated under microwave irradiation. From what we learn in our preliminary results, the retro-benzoin was best performed in the presence of thiazolium salts. So, a range of thiazolium salts was first screened as the pre-catalysts for the cleavage of α -ketol **12**. Firstly, we screened a series of commercially available thiazolium salts (Table 7). First, the α -ketol **12** was treated with thiamine pyrophosphate (ThPP) **66**, thiamine hydrochloride **67** and thiamine-derived thiazolium salt **68** in the presence of K_2CO_3 at 150°C under microwave irradiation.

Under these conditions, no conversion of α -hydroxyketone **12** was observed proving the incapacity of these catalysts to promote the retro-benzoin reaction (Table 7, entries 1-3). This phenomenon was explained by the degradation of these precatalysts. Indeed, thiazoliums **66-68** are stable until about 200°C as salts.²⁵⁹ However, they could be easily decomposed at elevated temperature (130 - 170°C) in basic medium at the methylene position, causing the degradation of thiazolium salts to thiazole and pyrimidine or aryl moieties.²⁶⁰ Better results were obtained with thiazolium salts **69**, **70** and **71**. On the one hand, 7% of conversion was observed with pre-catalyst **69** (Table 7, entry 4). On the other hand, 26% conversion was achieved with the precatalyst **70**. However, the selectivity of retro-benzoin products declined because of the generation of self-benzoin condensation products (Table 7, entry 5). This result indicates that the steric hindrance of *N*-alkyl chain could reduce the reactivity of the catalyst. Finally, when less bulky thiazolium salt **71** was used, the conversion reached 39% and the two aldehydes were obtained in 29% yield, along with 10% yield of the self-benzoin products **28** and **55** (Table 7, entry 6), then this precatalyst was selected for further optimization.

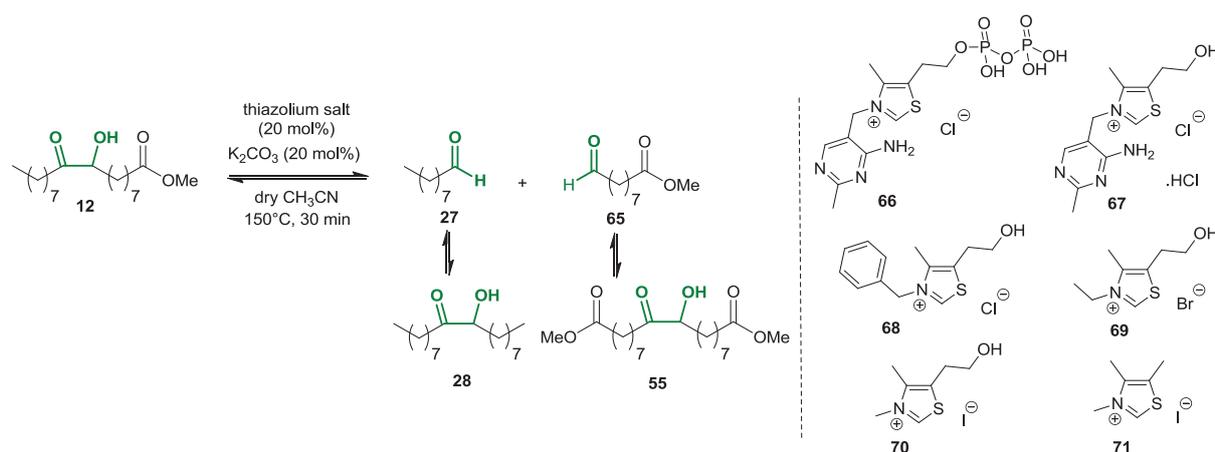
²⁵⁸ This work was done by Elsa Deruer during her master thesis in 2015.

²⁵⁹ A. Fulas, G. Vlase, T. Vlase, D. Onetiu, N. Doca, I. Ledeti, *J. Therm. Anal. Calorim.* **2014**, *118*, 1033-1038.

²⁶⁰ a) N. Shimahara, N. Nakajima, H. Hirano, *Chem. Pharm. Bull.* **1974**, *22*, 2081-2085; b) N. Shimahara, H. Asakawa, Y. Kawamatsu, H. Hirano, *Chem. Pharm. Bull.* **1974**, *22*, 2086-2090.

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Table 7: Screening of commercially available thiazolium catalysts for retro-benzoin^[a]



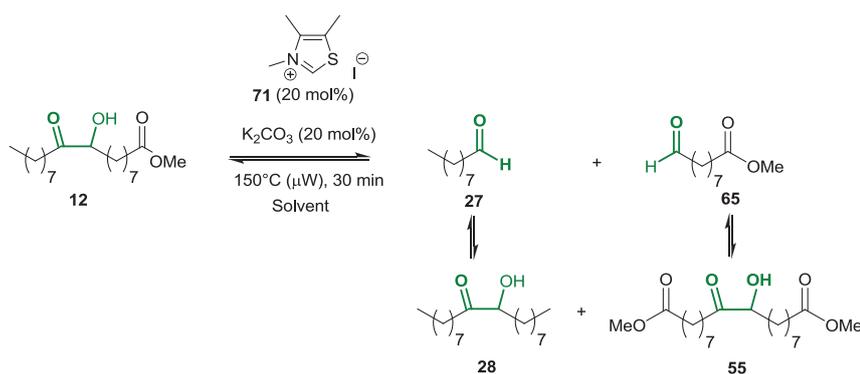
Entry	Thiazolium salt	Conv (%) ^[b]	Yield (%) ^[b]			
			27	65	28	55
1	66	0	0	0	0	0
2 ^[c]	67	0	0	0	0	0
3	68	0	0	0	0	0
4	69	7	7	7	0	0
5	70	26	22	22	4	4
6	71	39	29	29	10	10

[a] Conditions: Microwave tube, α -hydroxyketone **1** (1:1 mixture of regioisomers, 0.2 mmol), thiazolium salt (20 mol%), K_2CO_3 (20 mol%), dry CH_3CN (2 mL), 150°C (μW), 30 min. [b] Determined by GC using hexadecane as internal standard. [c] 40 mol% of K_2CO_3 was used.

A series of solvents was next evaluated under standard conditions in the presence of thiazolium salt **71** (20 mol%), K_2CO_3 (20 mol%) at 150°C under microwave irradiation (Table 8). DMF and EtOAc gave reasonable results with 18% and 15% conversion, respectively (Table 8, entries 2-3) whereas small conversions (<5%) were achieved when retro-benzoin condensation was examined in toluene or heptane (Table 8, entries 4-5). These results indicated that non-polar solvents were not able to promote the retro-benzoin process. Some ethereal solvents such as THF, 2-Me-THF, MTBE or DBE were tested but no positive result was observed (Table 8, entries 6-9). Finally, a saturated fatty ester such as methyl stearate was used as a bio-based solvent but no conversion was achieved under the standard condition and the starting material was recovered without any change.

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Table 8: Screening of solvents for retro-benzoin condensation^[a]



Entry	Solvent	Conv (%) ^[b]	Yield (%) ^[b]			
			27	65	28	55
1	CH ₃ CN	39	29	29	10	10
2	DMF	18	13	13	5	5
3	EtOAc	15	13	13	2	2
4	Toluene	4	4	4	0	0
5	Heptane	3	2	2	1	1
6	THF	0	0	0	0	0
7	2-Me-THF	0	0	0	0	0
8	MTBE	6	6	6	0	0
9	DBE	2	2	2	0	0
10	Methyl stearate	0	0	0	0	0

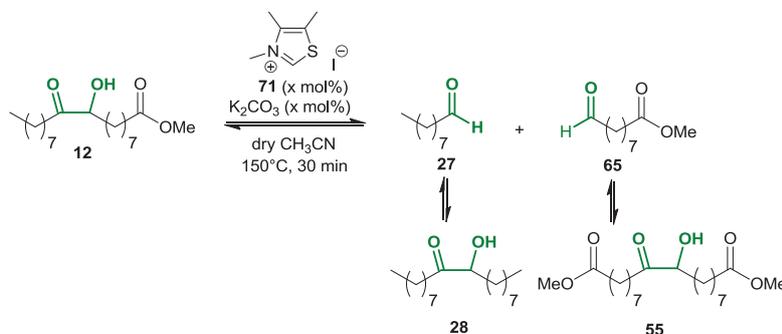
[a] Conditions: Microwave tube, α -hydroxyketone **12** (1:1 mixture of regioisomers, 0.2 mmol), thiazolium **71** (20 mol%), K₂CO₃ (20 mol%), dry solvent (2 mL), 150°C (μ W), 30 min. [b] Determined by GC using hexadecane as internal standard. THF = tetrahydrofuran, 2Me-THF = 2-methyl tetrahydrofuran, MTBE = methyl *tert*-butylether, DBE = dibutylether, DMF = dimethylformamide.

The catalyst loading was next studied at 150°C under standard condition with thiazolium **71** (Table 9). With 2 mol% of the precatalyst, only 7% conversion of **12** was observed (Table 9, entry 1). When the catalyst loading increased to 5 or 10 mol%, the better results were recorded with 23 and 33% conversion, respectively (Table 9, entries 2-3). However, by-products **28** and **55** were observed with 4 and 6% yield, respectively. Expectedly, when the loading of thiazolium salt **71** increased 20 mol%, the conversion of **12** reached 39% and 29% yield of two aldehydes were achieved with 10% of self-benzoin condensation products (Table 9, entry (Table 9, entry 4). No better result was observed with 40 mol% of precatalyst, indicating that the reaction reached a plateau and there is an equilibrium between benzoin and retro-benzoin condensation (Table 9, entry 5 and figure 8). Further

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attempt was tried in the presence of precatalyst (20 mol%) at 170°C, then 56% of conversion and 40% yield of desired aldehydes were achieved in 30 minutes (Table 9, entry 6). Prolonging the reaction's time to 60 minutes under the same condition gave a similar result (60% conv, 40% yield) (Table 9, entry 7).

Table 9: The screening of precatalyst and base loading for retro-benzoin condensation



Entry	Catalyst loading (mol%)	Base loading (mol%)	Conv (%) ^[b]	Yield (%) ^[b]			
				27	65	28	55
1	2	2	7	7	7	0	0
2	5	5	23	19	19	4	4
3	10	10	33	27	27	6	6
4	20	20	39	29	29	10	10
5	40	40	40	30	30	10	10
6 ^c	20	20	56	40	40	16	16
7 ^d	20	20	60	40	40	20	20

[a] Conditions: Microwave tube, α -hydroxyketone **1** (1:1 mixture of regioisomers, 0.2 mmol), thiazolium **71**, K_2CO_3 , dry CH_3CN (2 mL), 150°C, 30 min. [b] Determined by GC using hexadecane as internal standard. [c] 170°C, 30 min. [d] 170°C, 1h.

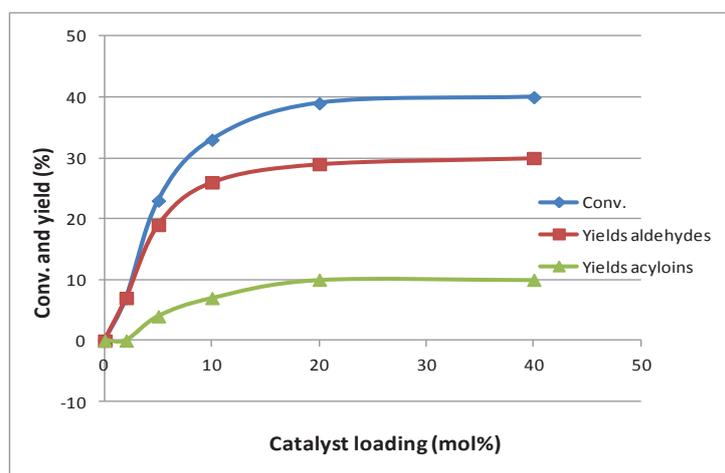


Figure 8: Influence of catalyst loading on the conversion and yields

In conclusion, we have developed a non-oxidative cleavage method for preparation of bio-aldehydes from fatty α -hydroxyketones, using a thiazolium salt **71** as a precatalyst under microwave irradiation. The retro-benzoin process occurs at 170°C and gives a 60% conversion and 40% of desired aldehydes after 1 hour. However, an equilibrium between benzoin and retro-benzoin condensation is established, then provides 20% yield of self-benzoin condensation products as the by-products. To shift this balance toward the formation of the aldehydes, some strategies were proposed such as reactive distillation or using aldehyde scavengers, etc.

3. Reactive distillation

In order to shift the equilibrium between benzoin condensation and retro-benzoin condensation of fatty α -hydroxyketones, the reactive distillation process is applied. In fact, the reactive distillation is a combination of chemical reaction and distillation with several advantages.²⁶¹ Firstly, the reactive distillation technology is energy-saving process because two steps can be combined and carried out in one device. Secondly, aldehyde selectivity could improve because the fast removal of more volatile products (aldehydes) from reaction medium could avoid the formation of two symmetrical α -hydroxyketones as well as the generation of other heavier by-products. Moreover, retro-benzoin condensation is exo-thermic reaction and the reaction heat could be used to evaporate part of surrounding liquid and help to distillation process more efficiently.

3.1 Preliminary results²⁶²

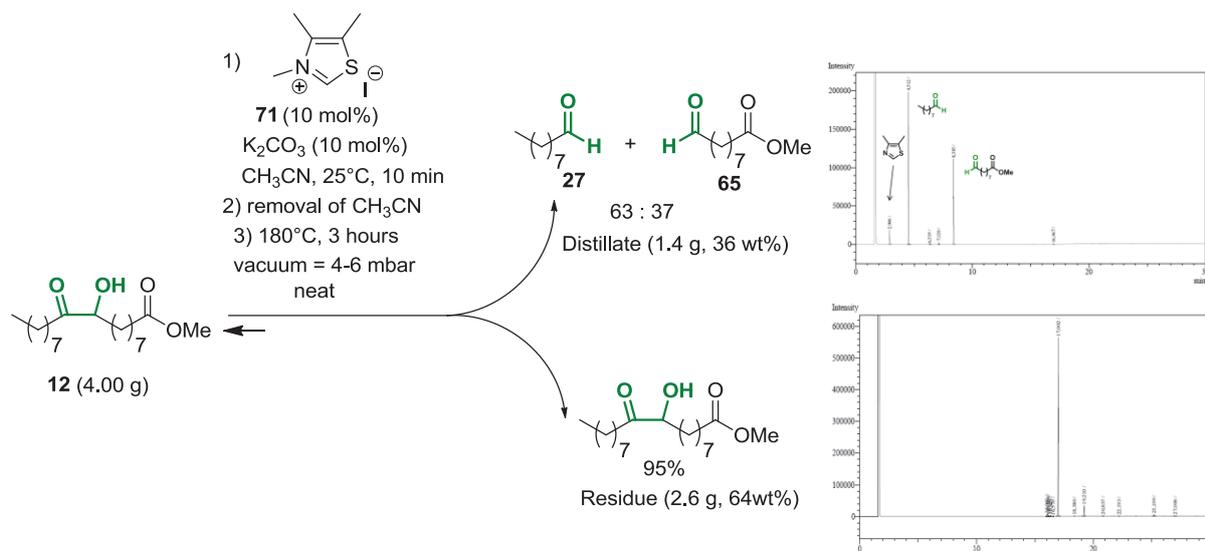
First, thiazolium salt **71** (10 mol%) was deprotonated in CH₃CN in the presence of K₂CO₃ (10 mol%), then the resulting solution was transferred into a flask containing the α -hydroxyketone **12** (4g, 12 mmol) and CH₃CN was removed under reduced pressure. After that, the flask was heated at 180°C under vacuum pressure (p =4-6 mbar) (Scheme 89). Encouragingly, 1.4 g of the mixture of two

²⁶¹ M. Sakuth, D. Reusch, N. Janowsky, *Ullmann's Encyclopedia of Industrial Chemistry* **2008**, DOI: 10.1002/14356007.c22_c01.pub2

²⁶² This work was done by Elsa Deruer during her master internship.

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aldehydes (36 wt%) was collected. Furthermore, no improved result was obtained when reaction's time was extended to more than 3 hours. Then, both distillate and residue were analyzed by GC. On the one hand, two aldehydes **27** and **65** were the major products in the distillate with the GC ratio 63:37. On the other hand, α -hydroxyketone **12** represented 95% as the major component in residue and several heavy by-products with a small quantity such as **55** were also found inside this mixture. However, there was a small peak observed on the GC chromatography (retention time = 2.9 minute). We hypothesized that the thiazolium salt **71** might be degraded under heating process. This proposal was confirmed by injecting the thiazole species in the GC and the same retention time was recorded.



Scheme 89: The reactive distillation for retro-benzoin of **12**, using thiazolium salt **71** as a pre-catalyst

Indeed, this phenomenon known as the retro-Menshutkin reaction was already observed with some imidazolium salts.²⁶³⁻²⁶⁴ Under thermal conditions, the ionic liquids were dealkylated by a strong nucleophilic agent such as halides, then the neutral imidazole species were released. In our case, this process might be accelerated under vacuum. In fact, methyl iodide is a volatile agent and was eliminated from system, thus leading to catalyst decomposition. Based on our knowledge, two degradation pathways of the catalyst were proposed (Scheme 90). First, thiazolydene species could be protonated back to thiazolium salt, then a nucleophilic agent could attack the *N*-alkyl group to release neutral thiazole species and the corresponding methylated nucleophile. Secondly, incomplete deprotonated thiazolium salt could directly decompose by nucleophilic substitution, then the C-N bond could be cleaved to give thiazole and methyl iodide.

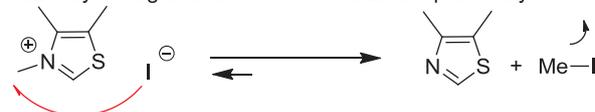
²⁶³ C. Maton, N. De Vos, C. V. Stevens, *Chem. Soc. Rev.* **2013**, 42, 5963-5977.

²⁶⁴ H. Ohtani, S. Ishimura, M. Kumai, *Anal. Sci.* **2008**, 24, 1335-1340.

Pathway a: degradation from the thiazolylidene species



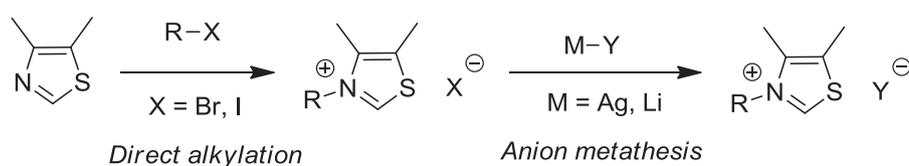
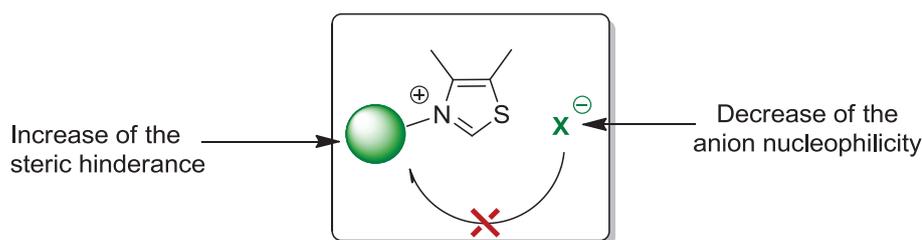
Pathway b: degradation from the thiazolium pre-catalyst


Scheme 90: Proposed mechanisms for the catalyst degradation

For further optimization, the pre-generation of thiazolium salt will be avoided and the precatalyst will be used as a reservoir for the thiazolylidene active species.

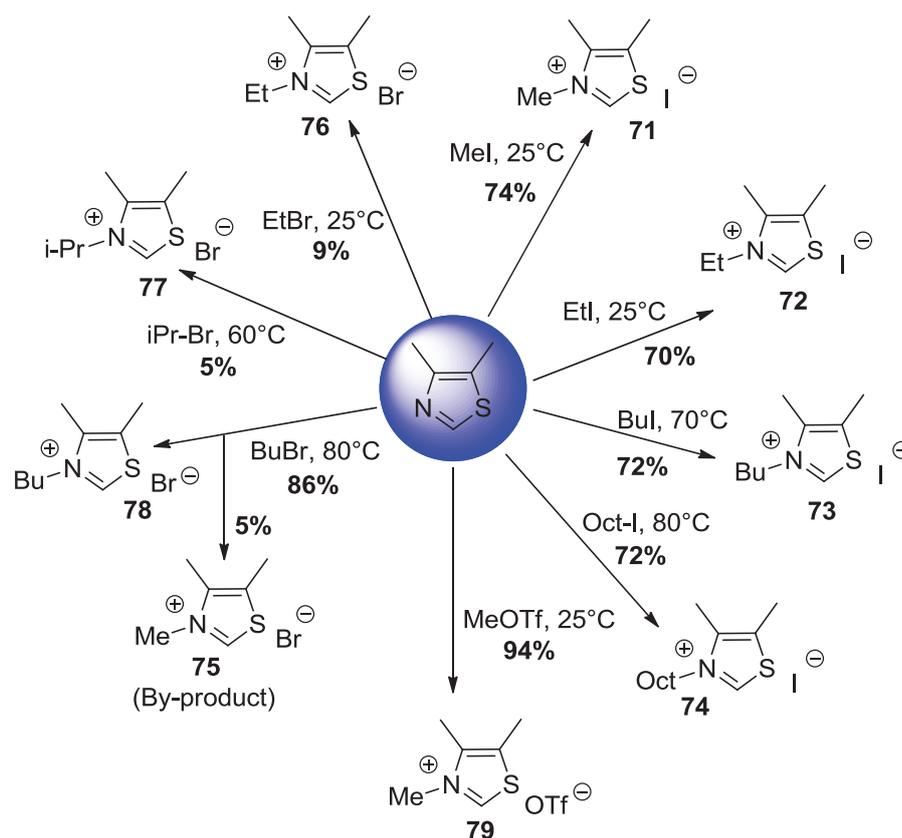
3.2 Synthesis of robust thiazolium salt²⁶⁵

Structural modifications of the thiazolium salt were next studied to increase its stability (Scheme 91). Two approaches have been envisaged: i) to increase the length chain or steric hindrance of *N*-alkyl chain; ii) to decrease the nucleophilicity of counter-anion.


Scheme 91: Two strategies to increase the stability of thiazolium salts

A first range of thiazolium salts was synthesized from 4,5-dimethyl thiazole with a series of alkyl halides (I⁻, Br⁻) or pseudohalide (OTf⁻) (Scheme 92). The use of alkyl iodide gave thiazoliums **71-74** with good yields (>70%) even if the length chain was increased from C1 to C8 while thiazolium bromides **76-77** were obtained with low yields. It might be caused by less reactive of alkylating agent (isopropyl bromide) or a volatile and unstable agent (EtBr). In the case of thiazolium salt **78**, 86% of desired product was achieved since the reaction was performed under solvent-free conditions at 80°C with an excess of butyl bromide. Under these conditions, 5% of precatalyst **75** was observed as by-product through elimination. Finally, the alkylation of thiazole with methyl triflate gave an excellent yield (94%) of thiazolium salt **79**.

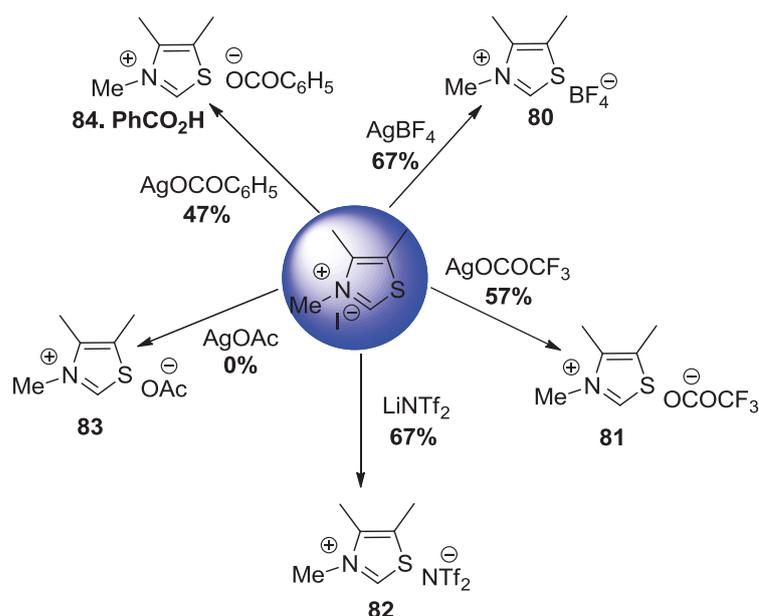
²⁶⁵ This work was done by Bah Souleymann under his master internship.



Scheme 92: The preparation of a series of thiazolium salts **71-79** by direct alkylation

A second range of thiazolium salts was prepared by counter-anion exchange of substrate **71** using potassium or lithium salts of charge-delocalized anion (Scheme 93). The synthesis of thiazolium **80**, **81** and **82** provided moderate isolated yields (57-67%). The thiazolium acetate **83** was also prepared to have a basic counter-anion which could help to avoid the use of an external base for the formation of the free-carbene. However, this product was decomposed quickly at room temperature. Indeed, several reports mentioned that imidazolium carboxylates (in particular acetate) could degrade rapidly at high temperature but these species were quite stable until 100-200°C.²⁶⁶ But the fact that thiazolium proton ($pK_a = 16.9$ in DMSO) is more acidic than imidazolium proton ($pK_a = 21$), led to the degradation of thiazolium species at room temperature. Finally, in order to substitute the acetate anion, a benzoate ion was used and thiazolium **84** was isolated with 47% yield.

²⁶⁶ M. T. Clough, K. Geyer, P. A. Hunt, J. Mertes and T. Welton, *Phys.Chem. Chem. Phys.* **2013**, *15*, 20480-20495.



Scheme 93: The preparation of thiazolium salts **80-84** by anion metathesis

Interestingly, the thiazolium salt **84** crystallized with one molecule of benzoic acid and the structure was confirmed by single crystal X-ray diffraction (Figure 9).

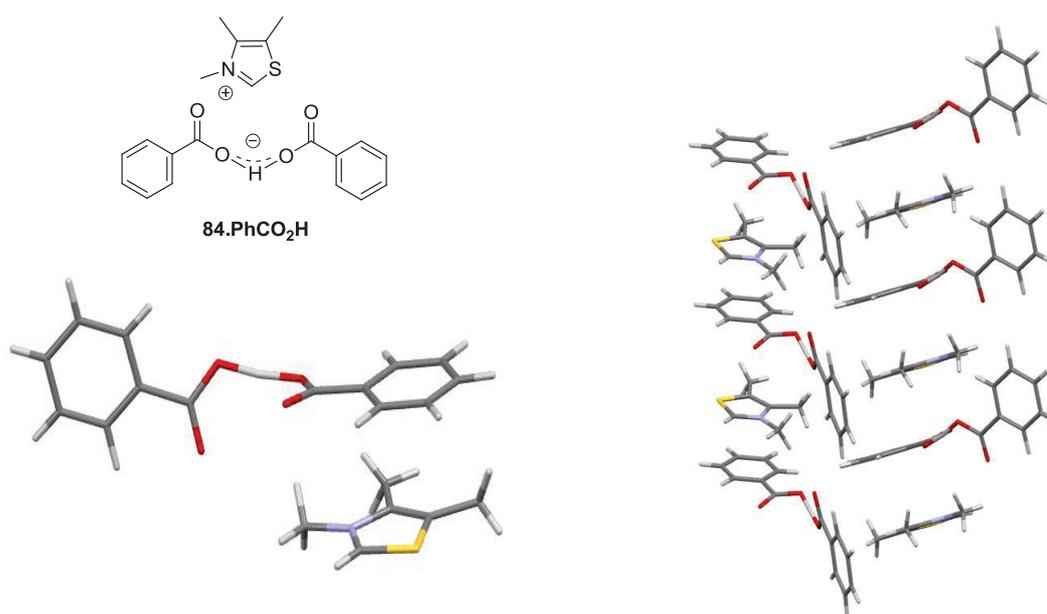


Figure 9: X-ray diffraction of thiazolium benzoate **84. PhCO₂H**

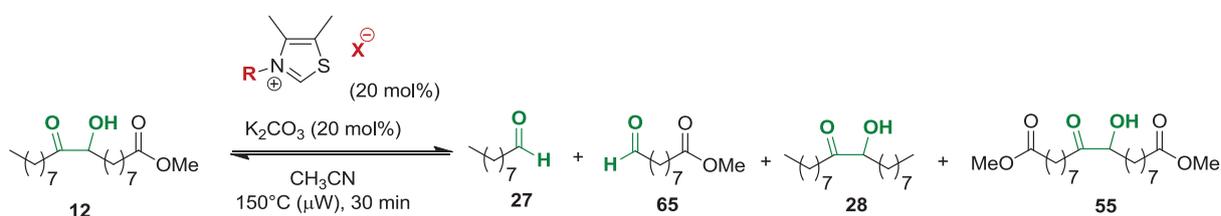
3.3 Reactivity of new thiazolium salts in the retro-benzoin condensation

The reactivity of a range of new thiazolium catalysts has been examined in the retro-benzoin condensation of α -ketol **12** under microwave irradiation (150°C, CH₃CN (0.1M), 30 min). The chain length of N-alkyl was the first evaluated using a series of thiazolium salts (Table 10). Increasing the length chain from C1 to C8 led to a rapid decrease of the conversion of reaction from 45% (for methyl) to 17% (for *n*-octyl) (Table 10, entries 1-4). The same trend was observed with the yield of two aldehydes (23% with *N*-methyl to 17% with *N*-octyl) and acyloin products **28** and **55**. With thiazolium **75**, a similar result was obtained and compared with pre-catalyst **72**, there was not too

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much difference in reactivity between the iodine and bromine anion (Table 10, entry 5). For thiazolium salt **76** bearing a *N*-isopropyl chain and a bromine anion, almost no conversion was observed, arguing that a bulky group could dramatically diminish the activity of catalyst (Table 10, entry 6).

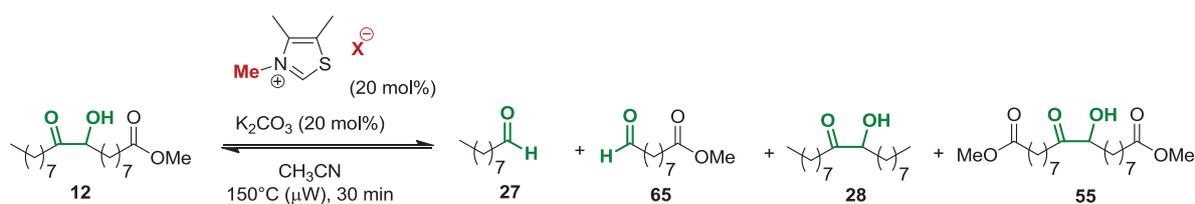
Table 10: Catalytic tests for retro-benzoin using thiazolium halide^[a]



Entry	Thiazolium salts		Conv. ^[b] (%)	Yield ^[b] (%)				
	R	X		27	65	28	55	
1	Me	I	71	45	23	23	11	11
2	Et	I	72	25	20	18	4	4
3	<i>n</i> -Bu	I	73	25	16	16	0	0
4	<i>n</i> -Oct	I	74	17	17	17	0	0
5	Et	Br	75	24	18	16	4	4
6	<i>i</i> -Pr	Br	76	3	2	1	0	0

[a] conditions: microwave tube, α -hydroxyketone **12** (1:1 mixture of regioisomers, 0.2 mmol), thiazolium salts (0.04 mmol), K_2CO_3 (0.04 mmol), dry MeCN (2 mL), $150^\circ C$, 30 min. [b] Yields were determined by GC using *n*-hexadecane as internal standard.

A range of thiazolium salts with a variety of counteranions was also investigated (Table 11). With a series of anions such as I^- , Br^- , OTf^- , BF_4^- and CF_3COO^- , the conversions reached around 34-39% and the yield of aldehydes **27-65** and self-benzoin products **28-55** were achieved around 23-29% and 8-10%, respectively (Table 11, entries 1-5). Therefore, the nature of anion has a small influence on the catalytic activity. The best candidate was recorded with triflate counter-anion. It has been noted that triflate is a charge-delocalized anion, then it prevents the nucleophilic substitution of the *N*-Me of the thiazolium species, leading to the increase the stability of precatalyst. A better conversion (52%) was observed with NTf_2^- anion. However, only around 20% of aldehydes and 3% of acyloin products were achieved, confirming that the reaction generated more by-products (Table 11, entry 6). Thiazolium benzoate **84** was next tested for retro-benzoin but only a low yield of aldehydes was obtained (Table 11, entry 7). Finally, an experiment using thiazolium catalyst **84** without external base was carried out and a similar result was obtained, indicating that benzoate anion could play the role of an internal base for the formation of thiazolylidene species (Table 11, entry 8).

Table 11: Catalytic investigation using *N*-methyl thiazolium salts^[a]


Entry	Thiazolium salt		Conv. ^[b] (%)	Yield ^[b] (%)			
	anion			27	65	28	55
1	I	71	39	29	29	10	10
2	Br	75	36	25	23	8	8
3	CF_3SO_3	79	39	26	24	10	10
4	BF_4	80	35	23	23	10	10
5	CF_3CO_2	81	34	25	25	9	9
6	$(CF_3SO_2)_2N$	82	52	21	18	3	3
7	$PhCO_2$	84.PhCO₂H	30	15	14	3	3
8 ^[c]	$PhCO_2$	84.PhCO₂H	36	20	17	4	4

[a] Conditions: microwave tube, α -hydroxyketone **12** (1:1 mixture of regioisomers, 0.2 mmol), thiazolium salts (0.04 mmol), K_2CO_3 (0.04 mmol), dry MeCN (2 mL), $150^\circ C$, 30 min. [b] Yields were determined by GC using n-hexadecane as internal standard. [c] No base was used in this condition.

3.4 Study of the thermal stability of thiazolium salts by TGA²⁶⁷

To deeper understand the decomposition of thiazolium salts, the thermal stability of precatalysts was evaluated *via* dynamic thermogravimetric analysis (TGA). Even if this method overestimates the thermal stability, it usually provides useful information on the short-term thermal stability of ionic liquids and is generally used for comparative purposes.²⁶⁸ The decomposition temperatures are reported in terms of T_{start} (the temperature at which the decomposition of the sample starts), T_{peak} (the peak temperature of the time derivative of the mass loss curve, $d(mass)/dt$), T_{onset} (the intersection of the zero mass loss baseline and the tangent line through T_{peak}) and T_{endset} (the intersection of the maximum mass loss baseline and the tangent line through T_{peak}). Moreover, contrary to imidazolium-based ionic-liquids, few TGAs were reported on thiazolium derivatives.²⁶⁹ First, the influence of the alkyl chain length on the stability was investigated with a series of thiazolium iodides **71-74** and dynamic TGAs were measured under nitrogen at a heating rate of $20^\circ C \cdot min^{-1}$ (Figure 10). In fact, there is no significant different between methyl and octyl chain and almost all TGA curves were superimposed, indicating that there was no influence of the length chain.

²⁶⁷ This work was done with the help of Dr Claire Negrell at the University of Montpellier.

²⁶⁸ C. Maton, N. De Vos, C. V. Stevens, *Chem. Soc. Rev.* **2013**, *42*, 5963-5977.

²⁶⁹ Q. Yan, H. Zang, C. Wu, J. Feng, M. Li, M. Zhang, L. Wang, B. Cheng, *J. Mol. Liq.* **2015**, *204*, 156-161.

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However, there was a slightly decrease of T_{onset} when the length chain was increased, confirming the drop of reactivity. This result is in accordance with the behavior of imidazolium salts.²⁷⁰

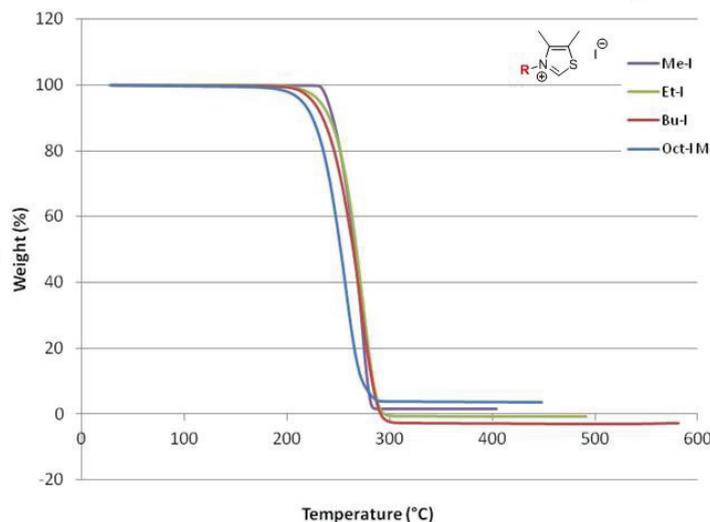


Figure 10: Dynamic TGA curves of thiazolium iodides 71-74

A second range of N-methyl thiazolium salts were next studied by TGA (Figure 11). Halide anions such as I and Br display very similar behavior with comparable T_{onset} , T_{peak} and T_{endset} (Table 12). It has been clearly seen that fluorine substituted anion gave a significant difference. While CF_3CO_2 anion reduces the thermal stability compared to halides, the use of BF_4 , OTf and NTf_2 anions increases the decomposition temperature of at least 100°C.

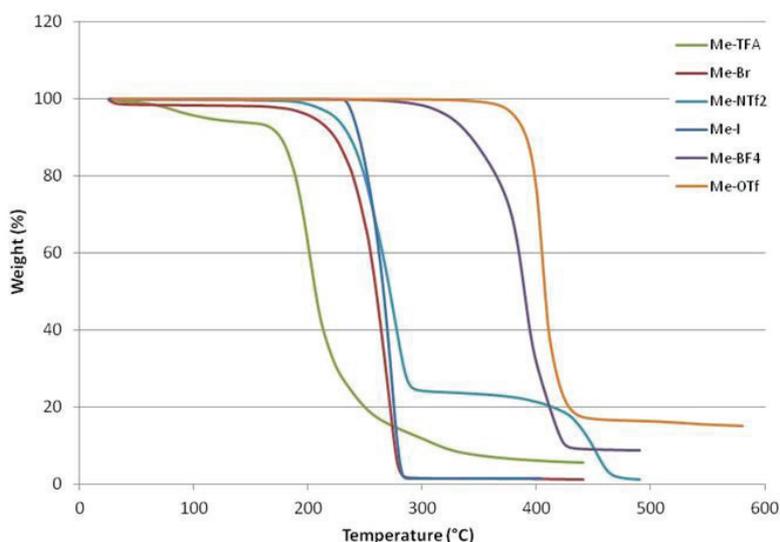


Figure 11: Dynamic TGA of N-methyl thiazolium salts

Noteworthy, the NTf_2 anion, which is usually giving the best thermal stabilities in the imidazolium series,²⁶⁸ showed two degradation waves in our case. It could be probably explained by

²⁷⁰ J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker, R. D. Rogers, *Green Chem.* **2001**, 3, 156–164.

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two different mode of degradation, one from the thiazolium cation and other one from the NTf₂ anion. These results show that the overall thermal stability of thiazolium salts is mainly governed by the nature of the anion and the relative robustness of these species could be ranked as follows: OTf > BF₄ > NTf₂ > I > Br > CF₃CO₂. Finally, thiazolium triflate **79** was found to be the more stable precatalyst with a degradation temperature of about 395°C.

Table 12: Thermal properties of thiazolium salts

Entry	Thiazolium salt			T _m (°C)	T _{onset} (°C)	T _{peak} (°C)	T _{endset} (°C)
	R	X					
1	Me	I	71	220-226	252	273	280
2	Et	I	72	130-132	249	273	287
3	<i>n</i> -Bu	I	73	74-78	244	273	287
4	<i>n</i> -Oct	I	74	62-66	232	259	272
5	Me	Br	75	170-174	242	273	279
6	Me	CF ₃ SO ₃	79	72-76	395	405	416
7	Me	BF ₄	80	158-162	367	390	409
8	Me	CF ₃ CO ₂	81	93-97	185	203	229
9	Me	(CF ₃ SO ₂) ₂ N	82	255-259	243	276	287
					428	454	464

[a] All TGA experiments were performed under an N₂ atmosphere T_m: melting temperature; T_{onset}: intersection of the zero mass loss baseline and the tangent line through T_{peak}; T_{peak}: peak temperature of d_(mass)/d_t curves; T_{endset}: intersection of the maximum mass loss baseline and the tangent line through T_{peak}.

In conclusion, a wide range of thiazolium salts has been evaluated for the retro-benzoin condensation of α -hydroxyketone **12** under microwave irradiation (150°C, CH₃CN, 30 minutes). Among them, the thiazolium catalyst bearing with *N*-methyl chain and triflate anion exhibits a high stability and is potentially the best candidate for this non-oxidative cleavage method. The methyl chain is responsible for the high reactivity and the charge-delocalized anion triflate is accountable to high thermal stability of the precatalyst. Then, this thiazolium salt **79** was further used in reactive distillation under optimized conditions.

3.5 Re-investigation of the reactive distillation with robust thiazolium salt

The reactive distillation was re-investigated using the most promising catalyst **79** in term of thermal stability and reactivity. In the presence of thiazolium salt **79** (20 mol%) using K₂CO₃ (10 mol%) as an external base, α -hydroxyketone **12** was introduced at room temperature and heated at 180°C (to give a homogeneous solution). The cleavage of α -hydroxyketone **12** was performed at

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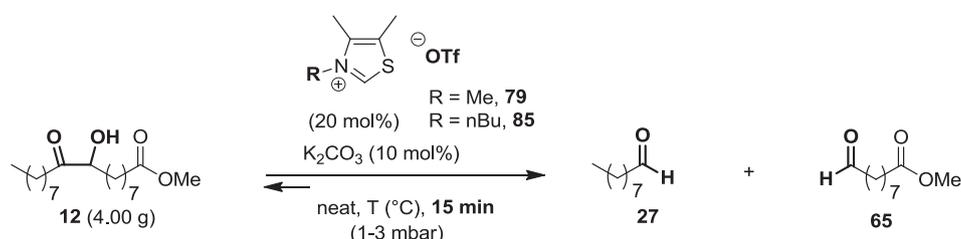
180°C under reduced pressure ($p = 1-3$ mbar) and gave an overall 75% weight yield for aldehyde products **27** and **65** after only 15 minutes (Table 13, entry 1). However, we have noticed that some of thiazolium salt **79** has been sublimated under these conditions. In order to avoid this inconvenience, thiazolium salt **85** bearing with *n*-butyl chain and triflate anion was synthesized in two-steps (alkylation and metathesis of counter anion) (Scheme 94).



Scheme 94: The synthesis of thiazolium salt bearing with *n*-butyl chain and triflate anion

Then, the cleavage reaction was carried out with pre-catalyst **85**. Satisfyingly, the reaction provided 75% weight yield of cleavage products and the yields of aldehydes **27** and **65** were calculated to 85 and 71%, respectively (Table 13, entry 2). Decreasing the temperature to 160°C gave the same proportion for the two aldehydes but the overall yield declined to 70% (Table 13, entry 3). Finally, the crude α -hydroxy ketone obtained from mono-oxidation of fatty vicinal diol (containing 83% of α -hydroxyketone **12**, the corresponding diketone (5%), the corresponding diol (3%) and nonanoic acid (6%)) was used as the starting material. The retro-benzoin condensation gave the two aldehydes **27** and **65** with 85 and 71% yield based on the purity of α -hydroxyketone **12**, emphasizing the robustness of the catalytic system (Table 13, entry 4).

Table 13: Non-oxidative cleavage of α -hydroxyketone **1** under reactive distillation conditions^[a]



Entry	R	Temp. ^[b] (°C)	Distillate				
			m 27+65 (g)	Yield 27+65 (wt%)	GC ratio 27+65	Yield 27 ^[c] (%)	Yield 65 ^[c] (%)
1	Me	180	3.00	75	61:39	84	70
2	<i>n</i> -Bu	180	3.07	75	60:40	85	71
3	<i>n</i> -Bu	160	2.82	70	60:40	80	67
4 ^[d]	<i>n</i> -Bu	180	2.48	75	62:38	85	71

[a] Conditions: distillation set-up, α -hydroxyketone **12** (1:1 mixture of regioisomers, 4.00 g), thiazolium salt (20 mol%), K_2CO_3 (10 mol%), neat, 1-3 mbar, 15 min. [b] Temperature of the oil bath. [c] Calculated yields based on calibration. [d] Crude starting material containing

α -hydroxyketone **12** (83%), the corresponding diketone (5%), the corresponding diol (3%) and nonanoic acid (about 6%).

To more understand the long-term thermal stability of the precatalyst during retro-benzoin condensation process, thiazolium salt **85** was evaluated by isothermal thermo-gravimetry analysis under nitrogen atmosphere (Figure 12).

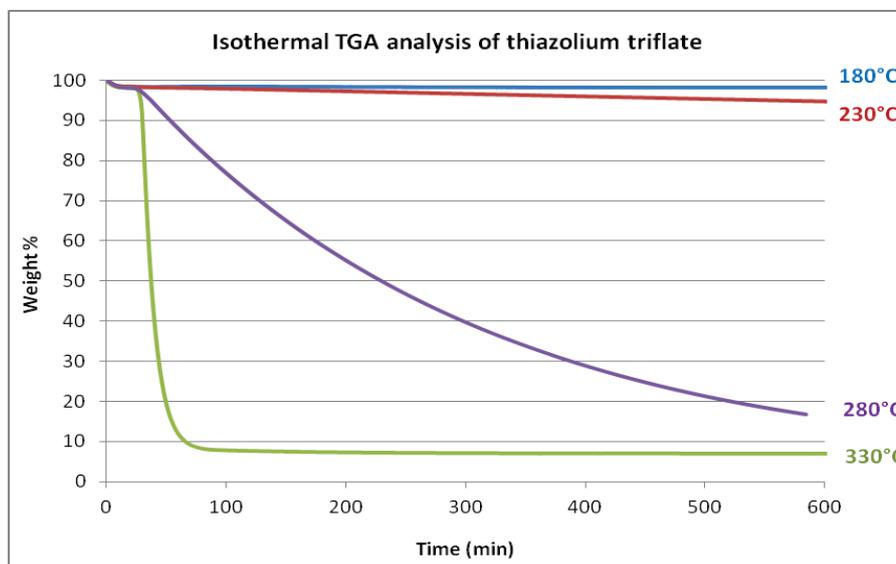


Figure 12: Isothermal TGA analysis of thiazolium triflate **85**

When isothermal temperature increases from 180 to 230°C both for 10 hours, the mass loss of **85** increases from 1.5 to 5%, probably due to the release of absorbed water inside the catalyst.. However, the degradation of thiazolium salt **85** increased to 83% when the isothermal TGA was performed at 280°C for 10 hours. Moreover, almost all of thiazolium salt decomposes after 2 hours when the sample is heated at 330°C. Finally, thiazolium salt **85** is stable below 230°C which is higher than the reaction temperature for retro-benzoin condensation process

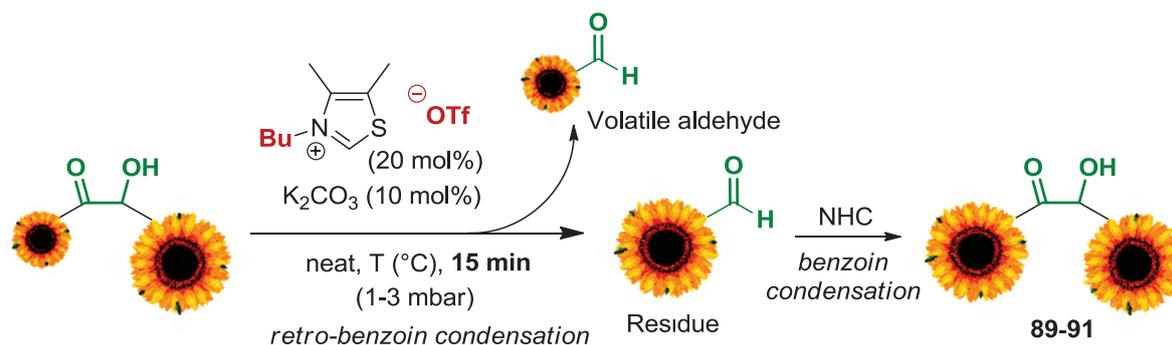
4. Scope for retro-benzoin condensation of fatty α -ketols

The scope for the retro-benzoin condensation of α -hydroxyketones derived from vegetable oils was next investigated under optimized condition (20 mol% of thiazolium salt **85**, 10 mol% of K_2CO_3 , 180°C, 15 minutes under vacuum) (Table 14). These starting materials were synthesized from the corresponding diols, using both of two methods developed: the mono-oxidation by $Pd(OAc)_2$ -neocuproine complex and the dehydrogenation by activated Ru/C (see Chapter II). First of all, symmetrical fatty α -ketols such as **28** and **55**, derived from the self-metathesis products of methyl oleate, were used. The cleavage of **28** gave 88% isolated yield of nonanal **27** while 80% yield of aldehyde ester **65** was afforded after retro-benzoin condensation of **55** (Table 14, entries 1-2).

This procedure was also used for other oleochemical substrates. Unsymmetrical fatty ketols **52** and **54**, originated from butyl oleate and 2-ethylhexyl oleate gave nonanal **27** with 82% and 93% yield, respectively (Table 14, entries 3-4). In these case, the bifunctionalized aldehydes could not

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distilled due to their high boiling point and undergo NHC-catalyzed self-benzoin condensation (Scheme 95).



Scheme 95: The formation of by-products **89-91** from the retro-benzoin condensation

As a result, symmetrical α -ketols **89** and **90** were isolated after column chromatography with 39 and 54% yield, respectively. A similar behavior was obtained with the fatty α -hydroxyketone **56**. Interestingly, an excellent yield (98%) of nonanal **27** was afforded and 30% yield of self-benzoin product **91** was obtained after purification (Table 14, entry 5).

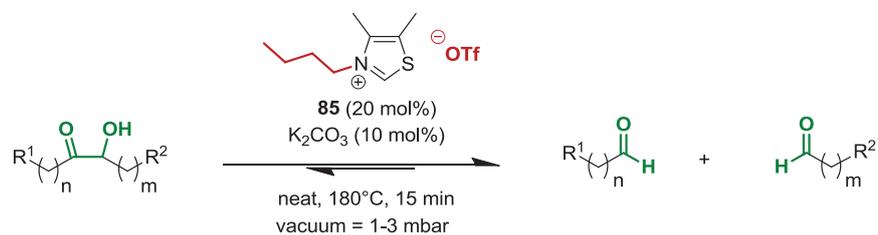
Then, the retro-benzoin of fatty α -ketol **57**, derived from methyl ricinoleate, was next investigated (Table 14, entry 6). However, only poor yield of (*R*)-3-methoxynonanal **87** and aldehyde-ester **65** were given. We hypothesized that the methoxy group was bulky enough to circumvent the addition of *N*-butyl thiazolium catalyst onto the carbonyl group. For this reason, thiazolium salt **79** was used and better yields of two aldehydes were obtained (15 and 30% yield). However, these results were not as good as those previously obtained. In fact, it should be noted that, in the presence of the methoxy group, the starting materials exist as a mixture of 4 inseparable isomers (NMR ratio = 25:18:21:36). Consequently, it is possible that one of these isomers reacts faster than the others with catalyst **79** to give retro-benzoin products. It also explained why some of the starting material was recovered from the residue. Then, tris-(α -hydroxyketone) **60**, synthesized from high-oleic sunflower oil (85% oleic content) and containing approximately 60% of α -ketol functionality, was also investigated under optimized conditions (Table 14, entry 7). Significantly, the retro-benzoin was performed with 25% yield of nonanal **27**, emphasizing that challenging substrates such as crude triglycerides could be cleaved under the conditions developed. This could open a new direction to valorize the cooking oil to value-added aldehydes which could be used in the preparation of bio-based surfactants, bio-polymers, etc. Finally, to further demonstrate the versatility of this method, benzoin **86** was examined for this transformation (Table 14, entry 8). Interestingly, an excellent yield (90%) of **88** was afforded using a vacuum pressure of 50 mbar.

In conclusion, we have developed the retro-benzoin condensation of fatty α -hydroxyketones. The reaction was conducted in the presence of a robust thiazolium salt **85** (20 mol%) and K_2CO_3 (10 mol%) at 180°C for only 15 minutes and gave a range of bio-aldehydes in good yields (up to 98%). Moreover, these conditions could be also applied for triglyceride derivatives as well as aromatic

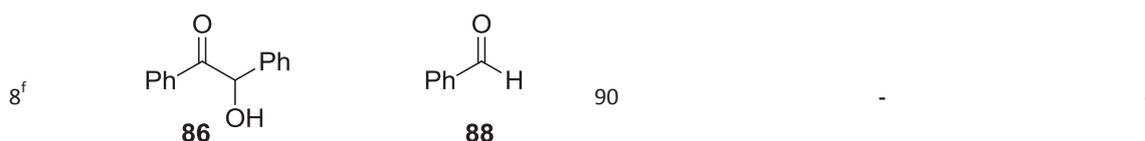
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substrates. In future, the use of non-volatile solvent should be considered to avoid the formation of heavy by-products or the reaction could be carried out in the continuous reactive distillation

Table 14: Scope for retro-benzoin condensation of α -ketol fatty derivatives^[a]



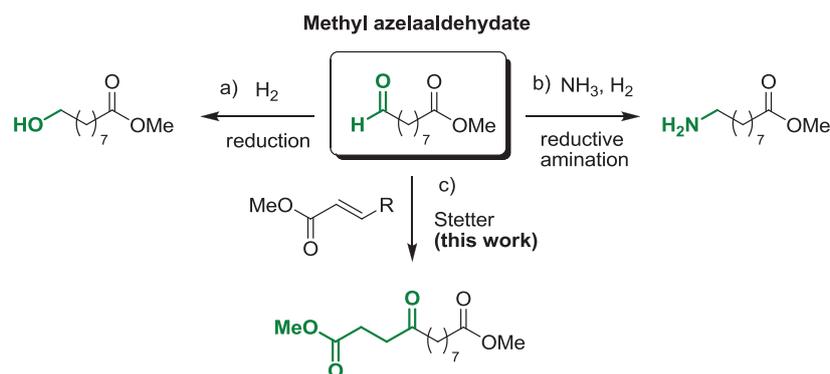
Entry	α -hydroxyketones	Yields ^[b] (%) of cleavage compounds in distillate	Yields ^[c] (%) of the main product in the residue
1 ^[d]		88	–
2		80	–
3		82	39
4		93	54
5		98	30
6		6 ^[c] (15) ^[c,e]	mainly starting material
		9 ^[c] (30) ^[c,e]	–
7		25 (25) ^e	–



[a] Conditions: distillation set-up, α -hydroxyketone (1:1 mixture of regioisomers), thiazolium salt (20 mol%), K_2CO_3 (10 mol%), neat, $180^\circ C$ (oil bath temperature), vacuum = 1-3 mbar, 15 min. [b] Isolated yields. [c] Isolated yields after purification by column chromatography. [d] The vacuum pressure was set at 10 mbar to avoid the distillation of the starting material. [e] Yield in brackets was obtained using catalyst **79**. [f] a pressure of 50 mbar was used.

5. Stetter reaction with Michael acceptor

The non-oxidative cleavage of methyl oleate-derived α -hydroxyketone, employing an organocatalyst thiazolium salt provided a mixture of two aldehydes: nonanal and methyl azelaaldehyde in good yields. Nonanal can be used as a fragrance in perfume industry or serve as the alkylating agent for the preparation of 100% biobased-surfactants through aldolisation²⁷¹ or reductive etherification of polyols²⁷² and carbohydrate derivatives.²⁷³ Comparatively, there are not so many studies on the valorization of methyl azelaaldehyde (Scheme 96). The aldehyde ester can be hydrogenated under hydrogen pressure in the presence of a palladium catalyst to give methyl 9-hydroxynonanoate, that could be further (co)polymerized to provide (co)-polyesters (Scheme 96, a)¹⁸⁴ while the reductive amination of the aldehyde ester with ammonia can give access to the corresponding amino ester that serve as a monomer for the production of polyamides (Scheme 96, b).²⁷⁴ The development of a complementary route to approach new bio-based monomers from this interesting chemical platform is highly desirable. In this context, we have studied the formation of various monomers through Stetter reaction (Scheme 96, c).



Scheme 96: Valorization of methyl azelaaldehyde to bio-based monomers

²⁷¹ a) B. Zhu, D. Belmessieri, J. F. Ontiveros, J.-M. Aubry, G.-R. Chen, N. Duguet, M. Lemaire, *ACS Sustainable Chem. Eng.* **2018**, *6*, 2630–2640; b) B. Zhu, G.-R. Chen, N. Duguet, M. Lemaire, *ACS Sustainable Chem. Eng.* **2018**, *6*, 11695–11703.

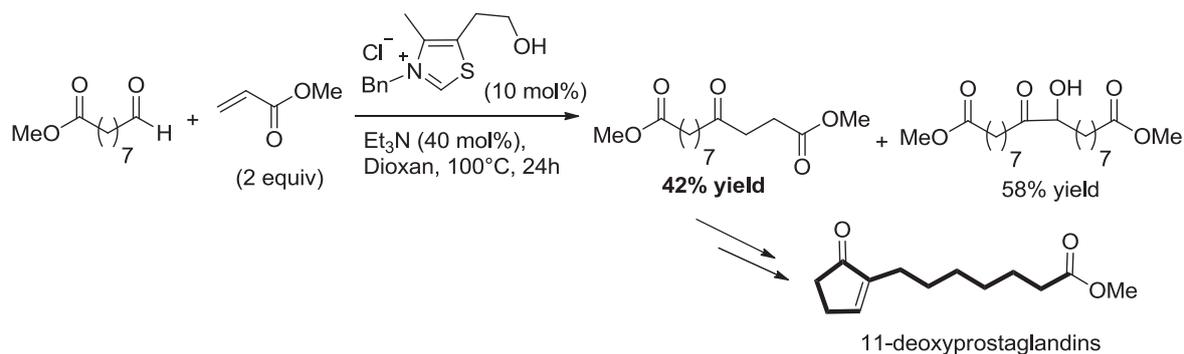
²⁷² Y. Shi, W. Dayoub, G.-R. Chen, M. Lemaire, *Green Chem.* **2010**, *12*, 2189–2195.

²⁷³ a) C. Gozlan, R. Lafon, N. Duguet, A. Redl, M. Lemaire, *RSC Adv.* **2014**, *4*, 50653–50661; b) Gozlan, C.; Deruer, E.; Duclos, M.-C.; Molinier, V.; Aubry, J.-M.; Redl, A.; Duguet, N.; Lemaire, M. *Green Chem.* **2016**, *18*, 1994–2004.

²⁷⁴ a) W. L. Kohlhaase, E. H. Pryde, J. C. Cowan, *J. Am. Oil Chem. Soc.*, **1970**, *47*, 183–188; b) K. Louis, E. Beauchene, L. Vivier, J.-L. Dubois, K. De Oliveira Vigier, Y. Pouilloux, *ChemistrySelect* **2016**, *1*, 2004–2008.

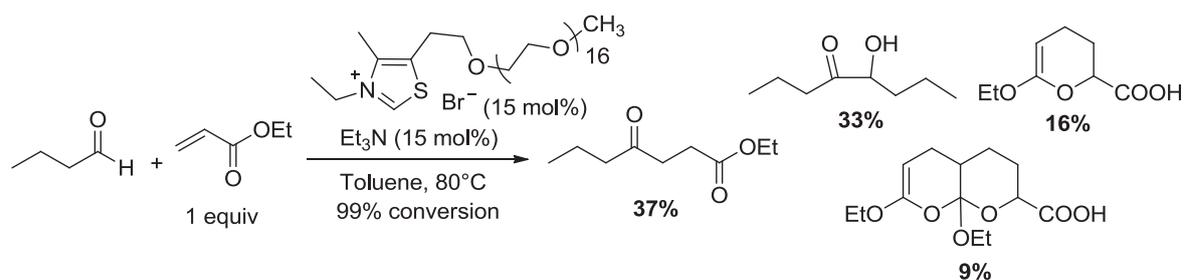
5.1 Stetter reaction with non-aromatic aldehydes

The Stetter reaction,²⁷⁵ i.e. the 1,4-addition of an aldehyde onto a Michael acceptor, employs *Umpolung* reactivity and has been extensively studied in both intra- and intermolecular versions (See *organocatalyst*, chapter 1). However, it has been by far less studied in the context of the valorization of biomass. To the best of our knowledge, there are only a few studies reported on the valorization of biomass *via* Stetter reaction. In an earlier work, Novak *et al.* reported the synthesis of a prostaglandin synthon *via* Stetter reaction between methyl azelaaldehyde and methyl acrylate.²⁷⁶ This reaction was catalyzed by a thiazolium salt and provided 42% of the Stetter adduct (Scheme 97). However, the corresponding symmetrical α -hydroxyketone was also obtained in 58% yield, indicating that the benzoin condensation is the main competing reaction.



Scheme 97: Stetter reaction between bio-fatty aldehyde and MA in the presence of thiazolium salt

More recently, Xie *et al.* have developed a polyether-substituted thiazolium ionic liquid for Stetter reaction.²⁷⁷ This reaction was conducted in the presence of thiazolium catalyst (15 mol%) at 80°C, employing butanal as a substrate. However, only 37% selectivity of Stetter adduct was obtained, due to the formation of several by-products such as benzoin condensation product, Diels-Alder adducts of Michael acceptor (Scheme 98).



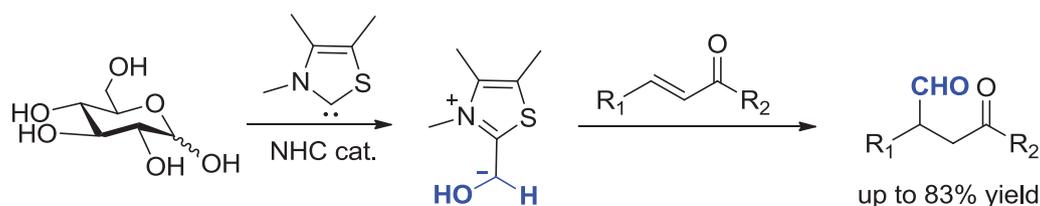
Scheme 98: Thiazolyldene-catalyzed Stetter reaction of butanal and ethyl acrylate

In 2013, Chi *et al.* have reported the use of the Stetter reaction to trap formaldehyde equivalents – generated from hexoses through retro-benzoin condensation with enones to give the corresponding β -formylketones in good yields, up to 83% (Scheme 87, see more details in literatures of retro-benzoin, chapter III).²¹³

²⁷⁵ H. Stetter, M. Schreckenberger, *Angew. Chem. Int. Ed.* **1973**, *12*, 81–81.

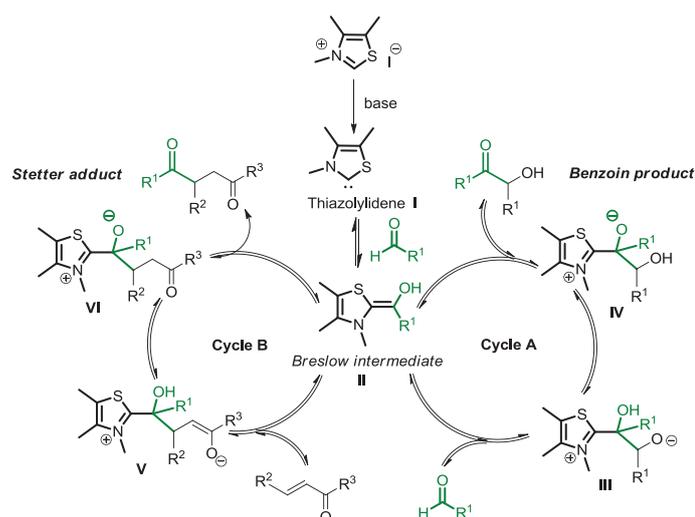
²⁷⁶ L. Novak, G. Baan, J. Marosfalvi, C. Szantay, *Chem. Ber.* **1980**, *113*, 2939–2949.

²⁷⁷ F. Yu, R. Zhang, C. Xie, S. Yub, *Green Chem.* **2010**, *12*, 1196–1200.



Scheme 99: Retro-benzoin/Stetter cascade for preparation of formyl ketones

From these literature precedents,²⁷⁶⁻²⁷⁷ a competing selectivity between the Stetter adduct and benzoin condensation product is the critical point of this reaction. In fact, both the Stetter and benzoin condensation reactions are correlated with the reactivity of the Breslow intermediate (Scheme 100). On the one hand, the nucleophilic addition of the Breslow intermediate onto the aldehyde, followed by hydride transfer, could release the symmetrical α -hydroxyketone as the benzoin condensation product (Scheme 100, cycle A). On the other hand, the addition of the Breslow intermediate onto the Michael acceptor provides the Stetter adduct (Scheme 100, cycle B). In most cases, the aldehyde is more reactive than the Michael acceptor, leading to the α -hydroxyketone as the main product. However, considering that the benzoin condensation is a reversible process while the Stetter reaction is not, the Stetter adducts can be produced as final products, as these species are usually thermodynamically favored.²⁷⁸ With aromatic aldehydes ($R^1 = \text{Ar}$), the reverse process can occur at low temperature (typically 25°C). Consequently, aromatic α -hydroxyketones, *i.e.* benzoin, fuoin can be used as aldehyde precursors for the Stetter reaction.²⁷⁹ In contrast, the α -hydroxyketones produced from aliphatic aldehydes ($R^1 = \text{alkyl}$), *i.e.* acyloins, are by far more stable than their aromatic analogues. Therefore, the retro-benzoin process can only occur at elevated temperature (typically 130°C) and can only be catalyzed by thiazolylidene species generated from the corresponding thiazolium salts, as reported by Miyashita,²⁵⁷ Chi²¹³ and our group^{Erreur ! Signet non défini.} then supported by DFT calculations.²⁸⁰



Scheme 100: Competing mechanism between Stetter and benzoin condensation

²⁷⁸ S. M. Langdon, C. Y. Legault, M. Gravel, *J. Org. Chem.* **2015**, *80*, 3597–3610.

²⁷⁹ a) G.-Q. Li, L.-X. Dai, S.-L. You, *Chem. Commun.* **2007**, 852–854; b) M. Padmanaban, A. T. Biju, F. Glorius, *Org. Lett.* **2011**, *13*, 98–101.

²⁸⁰ a) L. R. Domingo, P. Pérez, R. Contreras, *Tetrahedron* **2004**, *60*, 6585–6591; b) R. Appel and H. Mayr, *J. Am. Chem. Soc.* **2011**, *133*, 8240–8251.

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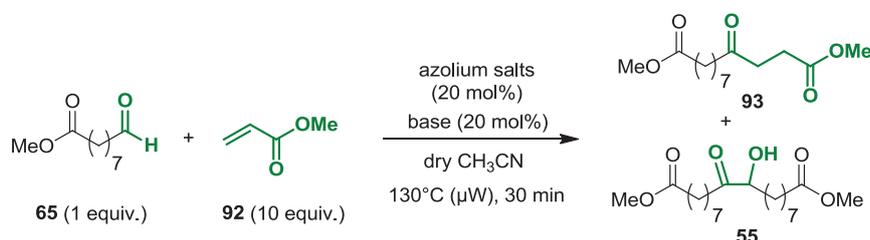
Herein, we would focus on the 1,4-addition of methyl azelaaldehyde onto a range of Michael acceptors to give bi-functionalized products that could serve as new bio-based monomers.

5.2 Results and discussion

Methyl azelaaldehyde was prepared through retro-benzoin condensation of α -hydroxyketone **12** and methyl acrylate was chosen as the model Michael acceptor for the first optimization.

The reaction was first screened in the presence of a range of azolium salt. The reaction was conducted in dried acetonitrile under microwave irradiation at 130°C (Table 15). After 30 minutes, the reaction with commercially available thiamine-derived thiazolium salt **94** gave a moderate conversion (59%) and Stetter adduct was obtained with only 27% yield (Table 15, entry 1). Under these conditions, the symmetrical α -hydroxyketone **55** was also formed with 18% yield. With our home-made thermally robust thiazolium triflate **85**, the conversion was improved to 89% and Stetter product was also obtained with 48% yield (Table 15, entry 2). A slightly better result was observed with commercially thiazolium salt **71**, providing Stetter adduct in 50% yield (Table 15, entry 2). Finally, triazolium salt **95**, used as negative control, gave no Stetter product and only yielded the self-aldolisation of aldehyde, confirming again the superiority of thiazolylidene species to catalyze the desired transformation (Table 15, entry 4). From these results, thiazolium salt **71** was selected as a precatalyst for further optimization.

Table 15: The screening of azolium salt for Stetter reaction^[a]



Entry	NHC precatalysts	Conversion (%) ^b	Yield of 93 (%) ^b	Yield of 55 (%) ^b
1	94	59	27	18
2	85	89	48	28
3	71	92	50	33
4	95	56	-	-

[a] Conditions: microwave tube, aldehyde **65** (1 equiv., 1 mmol), **92** (10 equiv.), azolium salt (20 mol%), K₂CO₃ (10 mol%) for

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precatalyst **71**, **85** and **94** or *t*-BuOK (20 mol%) for precatalyst **95**, dry CH₃CN (1.5 mL), 130°C (μ W), 30 min; [b] the conversions and yields were determined by GC using hexadecane as internal standard.

The effect of temperature was next studied on the Stetter reaction between aldehyde **65** and methyl acrylate **92** under microwave activation (Figure 13). From 110 to 130°C, an increase in conversion of aldehyde **65** and yields in Stetter product **93** and α -hydroxyketone **55** was observed. However, both the conversion and the yields declined above 130°C. This phenomenon could be attributed to the degradation of the thiazolium precatalyst **71** under these relatively harsh conditions. Consequently, further optimization was carried out using 130°C as the optimal temperature.

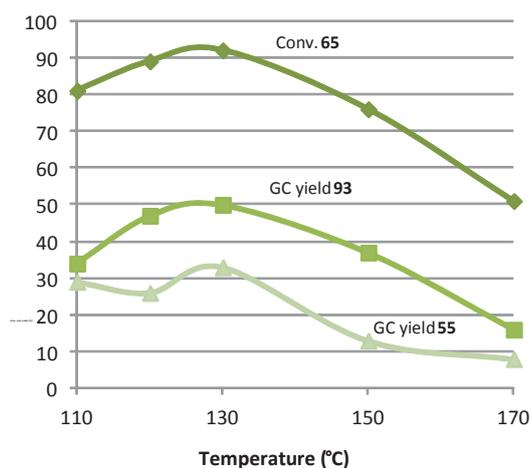
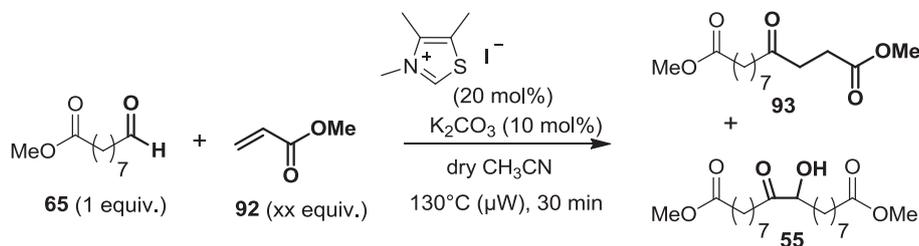


Figure 13: Effect of the temperature

The effect of the quantity of Michael acceptor **92** has then been next studied (Table 16). As expected, the yield in Stetter product **93** progressively increased between 2.5 and 10 equivalents of methyl acrylate (Table 16, entries 1-3). Further increase to 15 equivalents did not lead to significant improvement, as the selectivity only increased slightly (Table 16, entry 4). Consequently, 10 equivalents of methyl acrylate were selected as a good compromise. Finally, increasing the reaction time under our best conditions did not improve significantly the results.

Table 16: Screening of the quantity of Michael acceptor for Stetter reaction^[a]



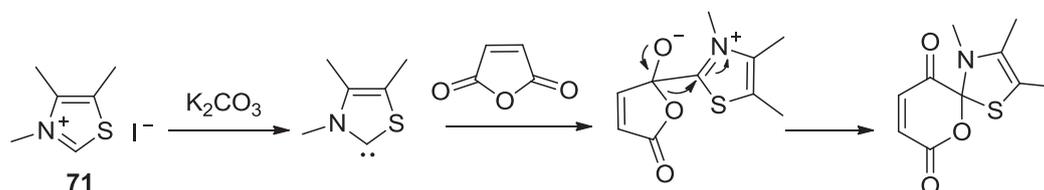
Entry	Quantity of 92	Conversion (%) ^b	Yield of 93 (%) ^b	Yield of 55 (%) ^b
1	2.5	93	23	52
2	5	91	37	43

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3	10	92	50	33
4	15	83	52	26

[a] Conditions: microwave tube, aldehyde **65** (1 equiv., 1 mmol), methyl acrylate, thiazolium salt **71** (20 mol%), K_2CO_3 (10 mol%), dry CH_3CN (1.5 mL), $130^\circ C$ (μW), 30 min; [b] the conversions and yields were determined by GC chromatography using n-hexanedecane as an internal standard.

Overall, under the best conditions, the desired Stetter product **93** was afforded with only 50% yield, while the undesired acyloin **55** was obtained in 33% yield. This moderate selectivity could be explained by the low electrophilicity of methyl acrylate. This assumption is supported by Domingo *et al.* in a DFT study aiming at classifying several Michael acceptors according to their reactivity toward nucleophilic addition.²⁸⁰ Keeping in mind that the objective is to synthesize aliphatic Stetter products with suitable functional groups for polymerization, a range of Michael acceptors was tested under optimized conditions (Table 17). Firstly, fumaric acid was evaluated for this transformation but no conversion was obtained with this Michael acceptor (Table 17, entry 1). This can be explained by its insolubility in acetonitrile and the fact that an equivalent of dicarboxylic acid could be reacted with the base as well as protonated the free carbene, then preventing the generation of active carbene species. Surprisingly, no reaction occurred with maleic anhydride that is known as one of the most electrophilic Michael acceptors (Table 17, entry 2).²⁸¹ In fact, the carbonyl moiety in maleic anhydride is more electrophilic than the one of the aldehyde. So, we hypothesized that the carbene formed from thiazolium **71** could directly add onto maleic anhydride instead of the aldehyde, thus giving a stable species and trapping the catalyst (Scheme 101).



Scheme 101: Potential intermediate formed through the trapping of thiazolyldiene by maleic anhydride

A similar intermediate, generated through an insertion of dialkoxycarbene onto maleic anhydride, was reported by Pole and Warkentin in 1995, confirming our hypothesis.²⁸²

Fumaronitrile **98** gave a high selectivity for the Stetter adduct (94%) but this result is not very representative considering that the conversion was very low (7%) (Table 17, entry 3). Acrylonitrile and methyl acrylate were the next probed under the optimized condition. After 30 min, both of them gave a good conversion (88-92%) but a moderate selectivity for the Stetter adduct was also obtained (72-79%), due to the similar electrophilicity of the carbon in mono-substituted ethylenes (Table 17, entries 4-5). Dimethyl maleate and dimethyl fumarate were also investigated but a difference in selectivity was observed with these two geometric isomers. On the one hand, dimethyl maleate provided a good conversion (88%) and a balanced formation of the benzoin and stetter product

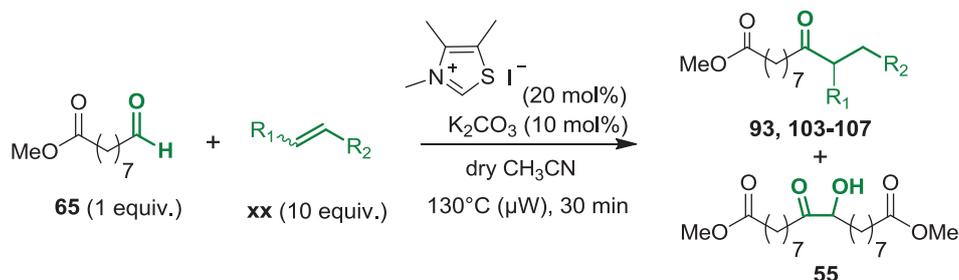
²⁸¹ D. S. Allgäuer, H. Mayr, *Eur. J. Org. Chem.* **2014**, 2956–2963.

²⁸² D. L. Pole, J. Warkentin, *Liesbig Ann.* **1995**, 1907-1914.

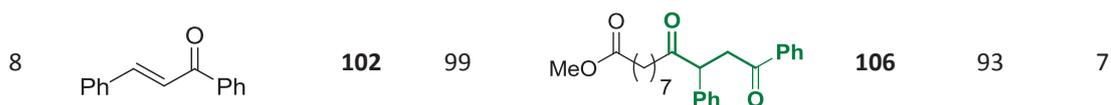
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(50:50) (Table 17, entry 6). On the other hand, dimethyl fumarate gave a better selectivity for triester product (85:15) (Table 17, entry 7). However, the conversion was remained at only 65%. Finally, chalcone **102**, a strong electrophilic Michael acceptor, was also evaluated under these conditions. Interestingly, the reaction provided a good selectivity for the Stetter product (93%) and the desired product **106** was isolated through column chromatography in a good yield (82%) (Table 17, entry 8).

Table 17: Stetter adduct/acyloin selectivity for a range of Michael acceptors



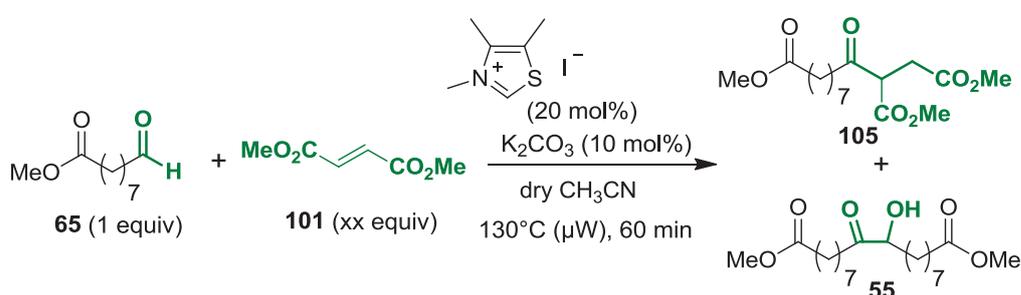
Entry	Michael acceptor	Conv (%) ^b	Stetter adduct	GC ratio (%) ^b		
				Stetter adduct	55	
1		96	-	-	-	-
2		97	-	-	-	-
3		98		103	94	6
4		99		104	72	28
5		92		93	79	21
6		100		105	50	50
7		101		105	85	15



[a] Conditions: microwave tube, aldehyde **65** (1 equiv., 1 mmol), Michael acceptor (**96-98**: 5 equiv., **92, 99-102**: 10 equiv.), thiazolium salt **71** (20 mol%), K_2CO_3 (10 mol%), dry CH_3CN (1.5-2 mL), $130^\circ C$ (μW), 30 min; [b] the conversions and ratios were determined by GC chromatography.

Encouraged by these results, the amount of dimethyl fumarate was studied with a prolonged time of 1 hour (Table 18). With only 2 equivalents of dimethyl fumarate, the selectivity remained quite stable but the conversion improved to 95%. Satisfyingly, when using 5 equivalents of dimethyl fumarate, the selectivity towards the Stetter adduct improved to 97% (Figure 14).

Table 18: Screening of the quantity of dimethyl fumarate for Stetter reaction^[a]



Entry	Quantity of 101 (equiv)	Conversion (%) ^b	GC ratio of 105 (%) ^b	GC ratio of 55 (%) ^b
1	2	95	84	16
2	5	96	97	3

[a] Conditions: microwave tube, aldehyde **65** (1 equiv., 1 mmol), dimethyl fumarate, thiazolium salt **71** (20 mol%), K_2CO_3 (10 mol%), dry CH_3CN (1.5 mL), $130^\circ C$ (μW), 1 hour; [b] the conversions and yields were determined by GC chromatography.

Interestingly, the reaction also gave two by-products in addition to the two expected products (Figure 14).

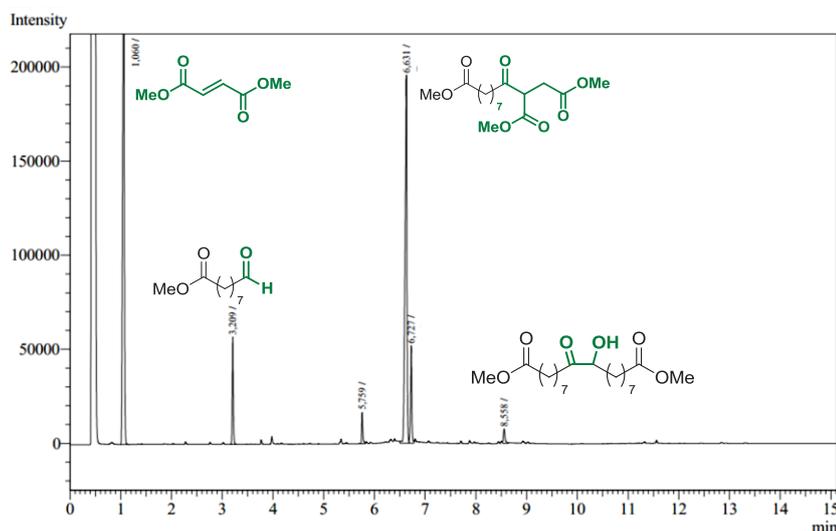
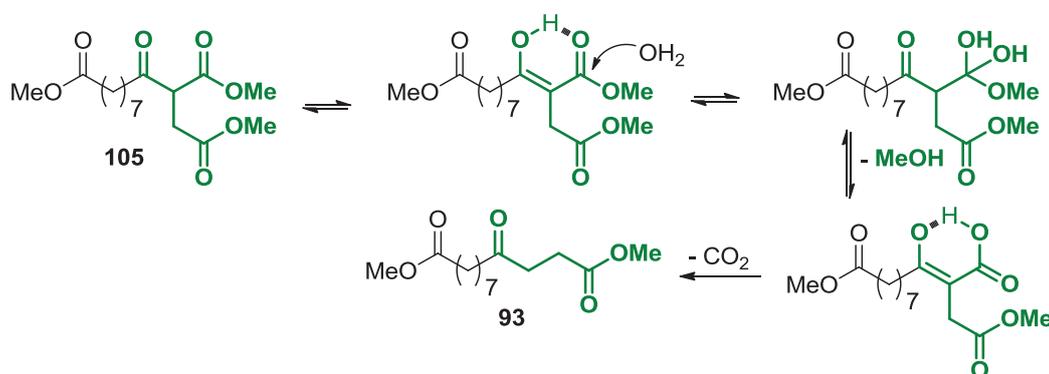


Figure 14: GC chromatogram of a crude reaction when using dimethyl fumarate as a Michael acceptor

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The product at 5.76 min has been characterized as the diester **93**, that is the exactly the same that the Stetter adduct formed by reaction between aldehyde **65** and methyl acrylate **92**. We thus hypothesized that Stetter adduct **105**, which is a β -ketoester, could undergo decarboalkoxylation in the presence of traces of water, thus giving product **93**. A similar reaction has been previously reported by Curran *et al.*, showing that microwaves play an important role in this process.²⁸³ In order to confirm this hypothesis, water (2.4 equiv) was voluntarily introduced in the crude after reaction and the mixture was heated at 180°C under microwave irradiation for an extra 30 min. Under these conditions, the initial 91:9 ratio between products **105** and **93** switched to 42:58 in favor of **93**, thus confirming our hypothesis (Scheme 102). Finally, considering that it is difficult to produce **93** with high selectivity from the direct Stetter reaction with methyl acrylate, the decarboalkoxylation of **105** offers an interesting alternative to access this diester.



Scheme 102: Mechanism proposal for the decarboalkoxylation of **105**

The second by-product at 6.7 min on the GC chromatogram of the crude mixture has been identified as methylene thiazolylidene species **108**. To account for the formation of this species, we proposed that dimethyl fumarate could undergo 1,4-addition of the thiazolylidene to furnish intermediate **107**, then followed by proton transfer (Scheme 103).

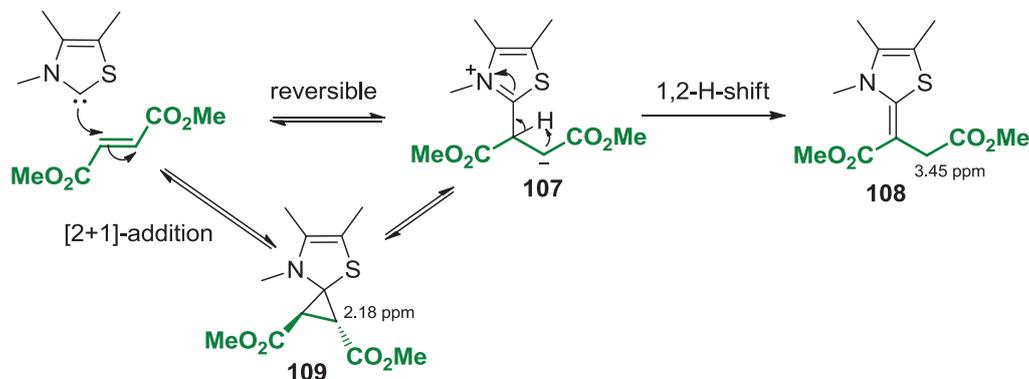
Another possibility is the [2+1] cycloaddition of dimethyl fumarate and the free carbene to give the spirocyclopropane derivative **109** as the primary product (Scheme 103). However, spirocyclopropane species is highly unstable due to ring strain and “push-pull” interaction of substitution pattern of spiro cyclopropane system. Consequently, this species could be converted to methylene thiazoline intermediate **108** through rearrangement. This structure has been assigned by ¹H, ¹³C-NMR analysis. Satisfyingly, the apparition of the characteristic proton at 3.45 ppm clearly indicated the formation of allylic proton inside methylene thiazolylidene **108**. Otherwise, a similar phenomenon was reported by Enders *et al* since triazolinylidene reacts with dimethyl fumarate or maleate, confirming our hypothesis.²⁸⁴⁻²⁸⁵ Moreover, this species was also elucidated by HR-ESI-MS and the measurement of exact mass ($[M+H]^+ = 272.0941$), was confirmed for molecular formula of C₁₂H₁₈NO₄S. Furthermore, we have also investigated the reaction under the same condition but in the absence of aldehyde **65**. After 1 hour, the species **108** was observed as a sole product. Otherwise, the

²⁸³ D. P. Curran, Q. Zhang, *Adv. Synth. Catal.*, **2003**, 345, 329–332.

²⁸⁴ D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem. Int. Ed.* **1995**, 34, 1021-1023.

²⁸⁵ D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Liebigs Ann.* **1996**, 2019-2028.

generation of methylene thiazolylidene intermediate **108** is not likely reversible. To confirm this hypothesis, the species **108** was used as a precatalyst instead of thiazolium salt **71**, with or without K_2CO_3 , under the optimized conditions. No Stetter adduct or benzoin product was obtained under these conditions, indicating that the species **108** is stable in our reaction condition and only dipole intermediate **107** could reverse to release the free carbene.



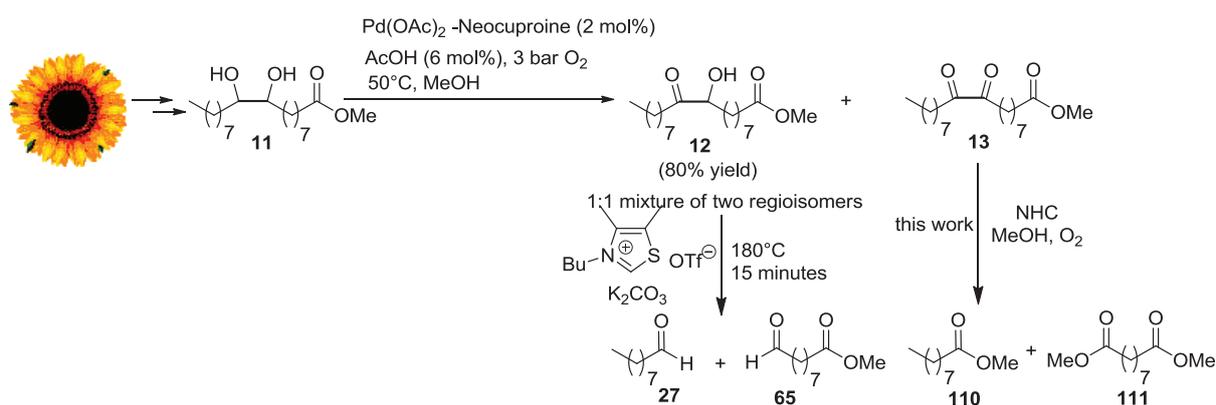
Scheme 103: Proposed mechanism for the formation of methylene thiazolylidene intermediate **108**

5.3 Conclusion

In summary, we have developed a new valorization route of vegetable oil-derived methyl azealdehyde through NHC-catalysed Stetter reaction. A wide range of Michael acceptors were evaluated under optimized condition and it was found that dimethyl fumarate gave the best result with 95% conversion and 97% selectivity for Stetter adduct. We have shown here that the selectivity between Stetter adducts and benzoin condensation product can be switched by using a strong electrophile. Furthermore, we have identified a new species **108** within the frame of this study. Finally, the di- or tri-esters obtained from this study could be used as chemical platforms in the preparation of bio-based polymers.

1. Introduction

In the previous parts, we have developed simple conditions to oxidize bio-sourced 1,2-diols to the corresponding α -hydroxyketones, using a catalytic system of Pd(OAc)₂ and neocuproine. This reaction was performed well in a range of fatty diols and gave good yields of desired α -ketols. However, in almost all of the cases, fatty 1,2-diketones are obtained as the only by-products. To valorize this by-product, we envisioned that the catalytic cleavage of fatty diketones using a thiazolium salt in the presence of oxygen could give the corresponding esters (Scheme 104). These esters are also really interesting for surfactants and polymer applications.



Scheme 104: Oxidative cleavage of fatty 1,2-diketones to the corresponding esters

2. State of Art

2.1 Preparation of fatty diketones

Fatty α -diketones have a range of applications for the synthesis of value-added compounds. They could be used for the preparation of heterocyclic substrates^{286,287} as well as for the cleavage to smaller building blocks in fine chemicals and pharmaceuticals.²⁸⁸ Conventionally, there are three major pathways to access these intermediates. The first approach to vicinal fatty diketone was through direct oxidation of unsaturated fatty acid derivatives. According to Jensen and Sharpless, the oxidation of methyl oleate using KMnO₄ as an oxidant occurs at 5°C and provided 40-50% yield of the desired products (Scheme 105, route A).²⁸⁹ However, this method suffers from diluted conditions (2 g of substrate per liter of solvent) and has a lack of selectivity. The second route for the preparation of fatty diketones that was reported by Doll *et al.*, involves the oxidation of epoxidized methyl oleate.⁶² This reaction requires a certain amount of Bi(III) triflate at 90°C, using DMSO as an oxidant (Scheme 105, route B). A quantitative conversion of epoxidized methyl oleate was observed after 2 hours. However, an inseparable mixture of monoketone and diketone (65:35) was obtained. Moreover, this

²⁸⁶ S. Furmeier, J. O. Metzger, *Eur. J. Org. Chem* **2003**, 885-893.

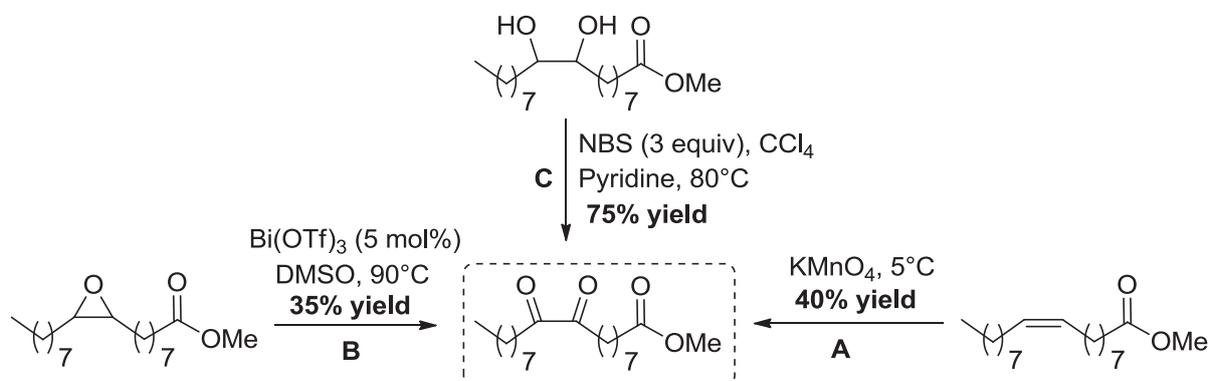
²⁸⁷ C. Richter, K. Schaepe, F. Glorius, B. J. Ravoo, *Chem. Commun.* **2014**, 50, 3204-3207.

²⁸⁸ V. Le Boisselier, C. Coin, M. Postel, E. Duñach, *Tetrahedron* **1995**, 51, 4991-4996.

²⁸⁹ H. P. Jensen, K. B. Sharpless, *J. Org. Chem.* **1974**, 39, 2314-2314.

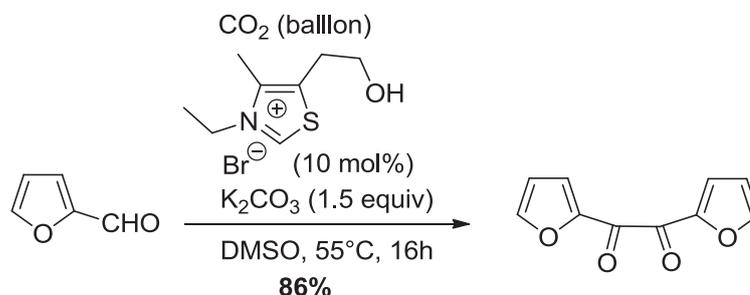
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method generates dimethyl sulfide that is a malodorous and toxic gas, then compromising the scale-up. The third pathway for the preparation of fatty α -diketones is the oxidation of fatty diols (Scheme 105, route C). The reaction was conducted in the presence of pyridine in CCl_4 , using NBS as an oxidant, thus providing a good yield of the desired product (75%).²⁹⁰ However, this method requires a big excess of dangerous oxidant such as NBS and is performed in a highly toxic solvent.



Scheme 105 : Traditional pathways for the synthesis of fatty α -diketones

More recently, Das *et al.* demonstrated a CO_2 -assisted the synthesis of diketones, derived from aromatic aldehydes (Scheme 106).²⁹¹ The reaction was conducted in the presence of catalytic amount of a thiazolium salt, using DMSO as an oxidant. This process provided good yields of α -diketone compounds (64-86% yield). However, this reaction releases the toxic gas (dimethyl sulfide) as a co-product and no example for aliphatic aldehyde was reported. Moreover, this method could not be applied to the functionalization of fatty acid derivatives.



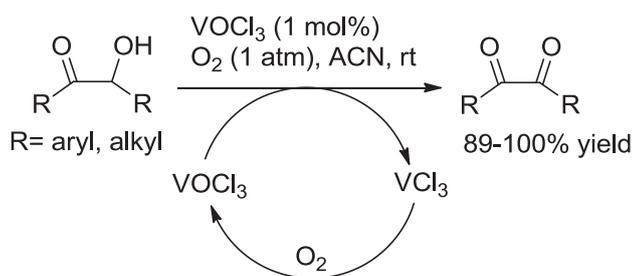
Scheme 106: CO_2 -assisted synthesis of diketones directly from aldehydes

In 1999, a preparation of unactivated diketones was reported by Kirihara *et al.* in the presence of Vanadium (V) catalyst (1 mol%) (Scheme 107).²⁹² This process involves two-step synthesis. The first step is benzoin condensation of aliphatic aldehydes in the presence of thiazolium salts to provide α -hydroxyketones in good yields. The second step is the oxidation of α -ketols at room temperature, using atmospheric oxygen and gave good yields up to 99% of corresponding 1,2-diketones.

²⁹⁰ J. M. Khurana, B. M. Kandpal, *Tetrahedron. Lett.* **2003**, *44*, 4909-4912.

²⁹¹ P. Hirapara, D. Riemer, N. Hazra, J. Gajera, M. Finger, S. Das, *Green Chem.* **2017**, *19*, 5356-5360.

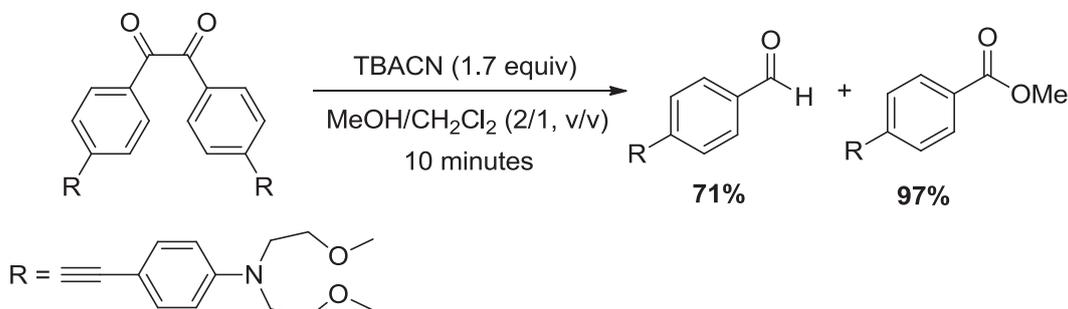
²⁹² M. Kirihara, Y. Ochiai, S. Takizawa, H. Takahata, H. Nemoto, *Chem. Commun.* **1999**, 1387-1388.



Scheme 107: Aerobic oxidation of α -hydroxyketone to corresponding diketone.

2.2 Cleavage of α -diketones

The cleavage of vicinal fatty diketones to the corresponding acids or esters has a great interest due to the applications of the smaller chemical platforms. They could be used directly as bio-lubricants, bio-herbicides, plasticizers as well as converted to bio-surfactants or bio-polymers. However, this field is underexploited. There are a few studies mentioning on the cleavage of vicinal diketones, using inorganic reagents. In 1958, Kwart and Baevsky claimed that the cyanide anion could catalyze the cleavage of aromatic diketones into corresponding aldehyde and ester in the presence of alcohols.²⁹³ However, only kinetic studies were given in this report. Recently, benzyl-cyanide reaction was reinvestigated by Sessler *et al.* to develop a selective cyanide indicator.²⁹⁴ They also showed that in the presence of stoichiometric amount of tetrabutyl ammonium cyanide, benzil derivatives could be cleaved to the corresponding aldehyde and ester in yield of 71 and 97%, respectively (Scheme 108).



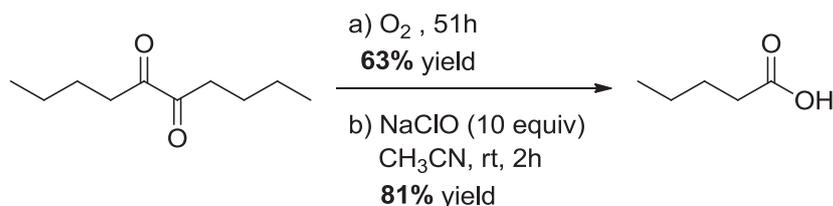
Scheme 108: Cyanide-catalyzed cleavage of benzil derivatives to the corresponding aldehyde and ester

Several studies recently mentioned the cleavage of diketones, employing the oxidizing agents such as sodium hypochlorite solution (NaClO) or oxygen. On the one hand, the cleavage of diketone using oxygen gives only moderate yield of corresponding acid (50% yield) and requires a long reaction time (51 hours) (Scheme 109, condition A). On the other hand, when bleach is used, good yields of corresponding acid were reported for both aromatic and aliphatic substrates (79-87% yield) (Scheme 109, condition B). However, a large quantity of sodium chloride was formed after this reaction, indicating the limitation of this method.^{288,295}

²⁹³ H. Kwart, M. Baevsky, *J. Am. Chem. Soc.* **1958**, *80*, 580-588.

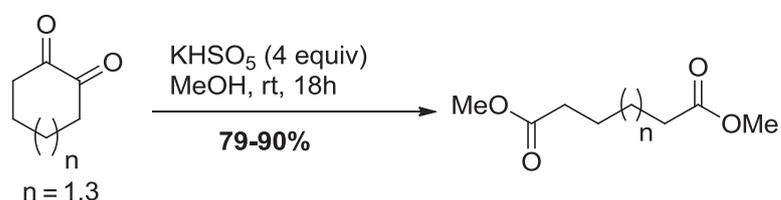
²⁹⁴ D.-G. Cho, J. H. Kim, J. L. Sessler, *J. Am. Chem. Soc.* **2008**, *130*, 12163-12167.

²⁹⁵ J. M. Khurana, P. Sharma, A. Gogia, *Org. Prep. Proced. Itl* **2007**, *39*, 185-189.



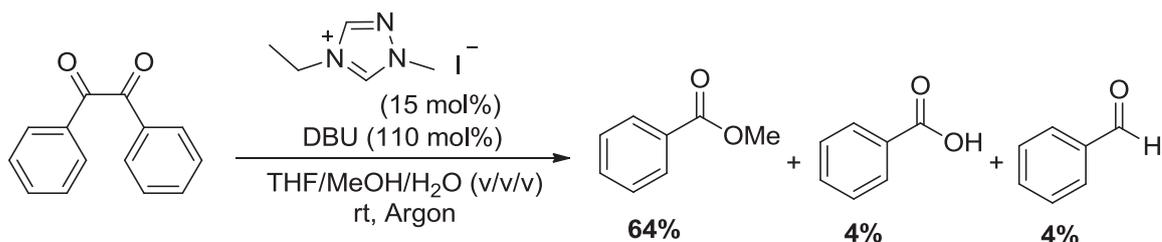
Scheme 109: Cleavage of 1,2-diketones to the corresponding acids in the presence of oxidizing agent

In 2004, an efficient method for oxidative esterification of cyclic diketones was presented by Borhan *et al.* The reaction was conducted in methanol at room temperature, using an excess of Oxone (4 equiv) (Scheme 110).²⁹⁶ In fact, this reaction involves a two-step synthesis. Firstly, the cyclic diketones could be converted to cyclic anhydride in the presence of oxone. Secondly, alcoholysis of the cyclic anhydride occurs in excess of alcohol at room temperature to give a good yield (up to 90%) of dimethyl ester. However, a large quantity of waste was generated, indicating the restriction of this method.



Scheme 110: Cleavage of cyclic diketones to the corresponding esters in the presence of Oxone

More recently, the cleavage of the aromatic diketones, using organocatalysts has also been reported. Reinvestigated by Connor *et al.*, the cleavage of benzil occurs in the presence of triazolium catalysts at room temperature.²⁹⁷ The reaction provided a yield of 64% for the corresponding methyl ester, in parallel with the formation of aldehyde or acid intermediates (Scheme 111).



Scheme 111: NHC-mediated non-aerobic cleavage of benzil to the corresponding ester

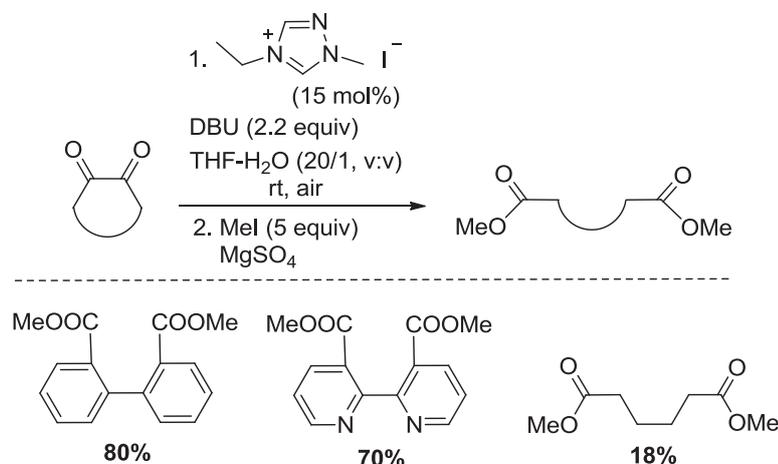
This strategy has also applied for the cyclic diketone. However, the process was conducted in two steps. The first step involves the oxidation of diketones into the corresponding acids, then the second step converts the acids to the corresponding methyl esters in the presence of methyl iodide. The reaction was carried out in mild conditions and provided good yields of aryl esters (66-82%)

²⁹⁶ J. Yan, B. R. Travis, B. Borhan, *J. Org. Chem.* **2004**, 69, 9299-9302.

²⁹⁷ E. G. Delany, C.-L. Fagan, S. Gundala, K. Zeitler, S. J. Connon, *Chem. Commun.* **2013**, 49, 6513-6515.

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(Scheme 112).²⁹⁸ However, only 18% yield of dimethyl adipate was obtained for the cleavage of 1,2-dioxocyclohexane, implying the restriction of this method for non-aromatic substrates.



Scheme 112: Triazolium-catalysed cleavage of cyclic diketones into corresponding esters

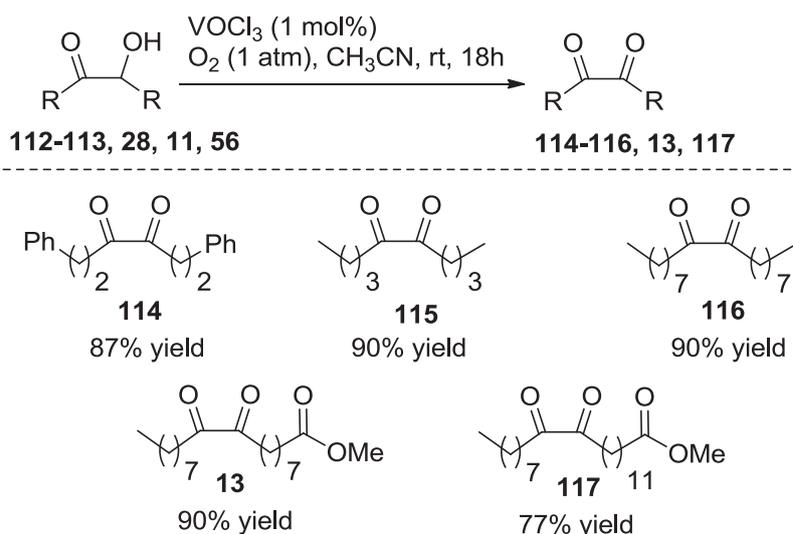
3. Results and discussion

Herein we would first describe the synthesis of vicinal diketones derived from vegetable oil derivatives that are considered as by-products from aerobic mono-oxidation of fatty 1,2-diols catalyzed by a complex of Pd(OAc)₂ and neocuproine. Then, the cleavage of fatty diketones is studied in the presence of cheap and abundant thiazolium salt.

3.1 Preparation of α -diketones

Initially, α -hydroxyketones were synthesized through benzoin condensation of aldehydes or mono-oxidation of vicinal diols, catalyzed by Pd(OAc)₂-neocuproine as described in chapter II. Then, inspired from the studies of Kirihara *et al.*, these α -hydroxyketone were oxidized under oxygen in the presence of VOCl₃ (1 mol%) (Scheme 113). The reaction was carried out in acetonitrile at room temperature (20°C). After 18 hours, the complete conversion was observed with good yields of desired products. On the one hand, the treatment of symmetrical α -hydroxyketones gave the corresponding diketones in 87-90% yield. On the other hand, bio-based diketone derived from unsaturated fatty acids (methyl oleate and methyl erucate) were isolated in 90% and 77% yield.

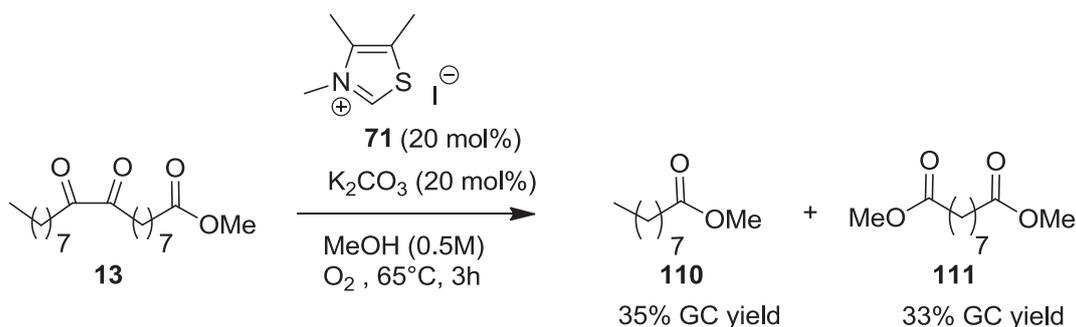
²⁹⁸ S. Gundala, C.-L. Fagan, E. G. Delany, S. J. Connor, *Synlett* **2013**, 24, 1225–1228.



Scheme 113: Scope for the preparation of α -diketones.

3.2 Organocatalytic cleavage of fatty diketones.

Encouraged by the results of Connon on the cleavage of aromatic diketone, catalysed by a triazolium salt, the organocatalytic cleavage of the fatty diketone derived from methyl oleate was investigated. The reaction was conducted at 65°C in the presence of a thiazolium catalyst (20 mol%), using oxygen as an oxidant (Scheme 114).



Scheme 114: Oxidative cleavage of fatty 1,2-diketones into the corresponding esters

Under these conditions, almost complete conversion of diketone **13** was observed after 3 hours. Then, methyl pelargonate **110** and dimethyl azelate **111** were achieved in moderate yields of 35% and 33%, respectively after GC titration using *n*-hexadecane as an internal standard. However, two heavier products **118** and **119** were also observed in the GC chromatogram at 10.1 and 10.9 min (Figure 15).

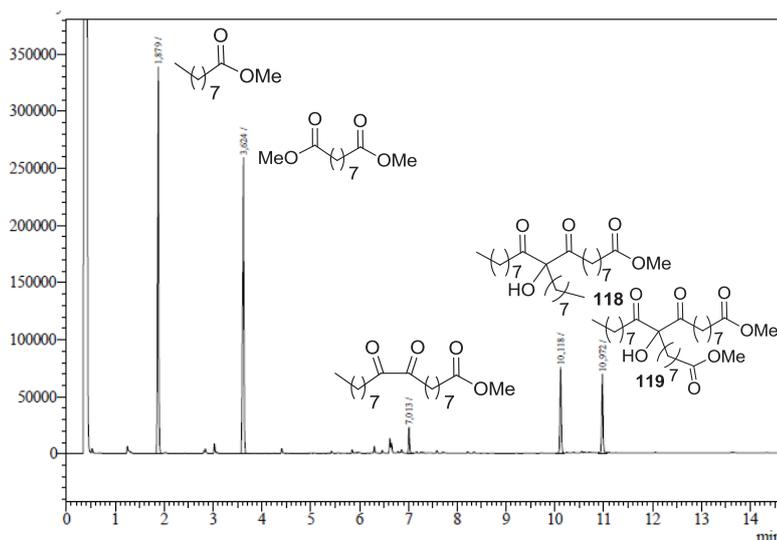
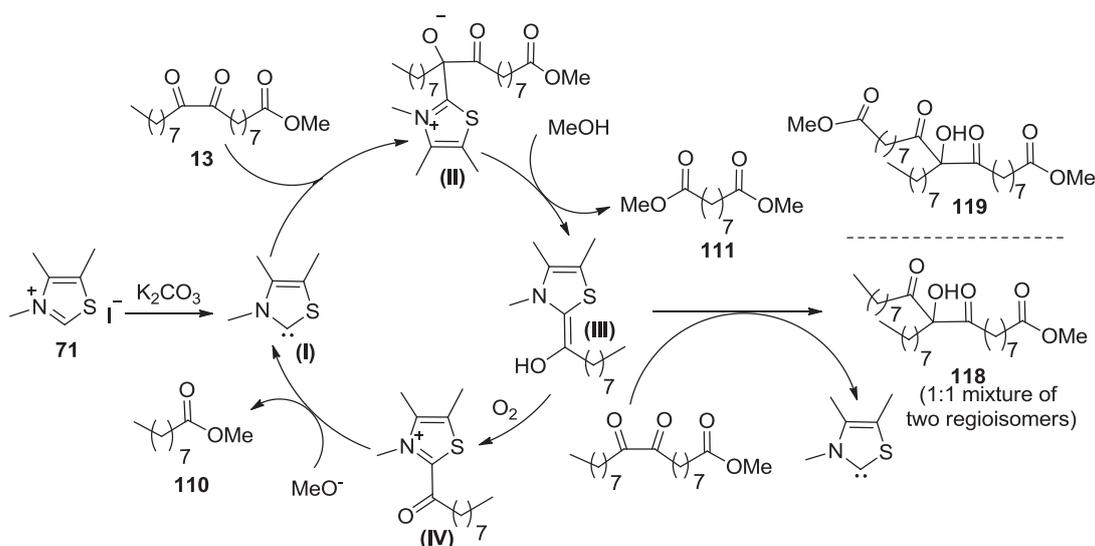


Figure 15: GC chromatogram of the oxidative cleavage of 1,2-diketone derived from methyl oleate

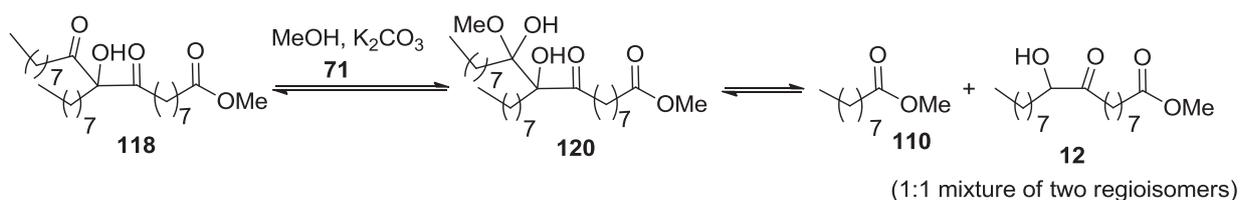
In fact, the formation of these by-products could be explained from a mechanism point of view (Scheme 115). The first step of this reaction is a deprotonation of thiazolium salt in the presence of an inorganic base such K_2CO_3 to generate the thiazolylidene species (I). This free carbene could attack the diketone **13** to form the intermediate (II) that could be cleaved in the presence of methoxide to release an ester and Breslow intermediate (III). Then, there are two possible pathways for the next transformation. On the one hand, the Breslow intermediate could be oxidized in the presence of oxygen to form the acyl carbene species (IV), then followed by nucleophilic addition of methoxide from methanol to liberate the second ester and free carbene. On the other hand, the Breslow intermediate (IV) could react with α -diketone **13** via acyl anion transfer to form the coupling products **118** and **119** that are presented in GC chromatogram at 10.1 and 10.9 minutes. Moreover, it should be noted that each compound is a mixture of two regioisomers that overlap on the GC chromatogram.



Scheme 115: Proposed mechanism for oxidative cleavage of α -diketone

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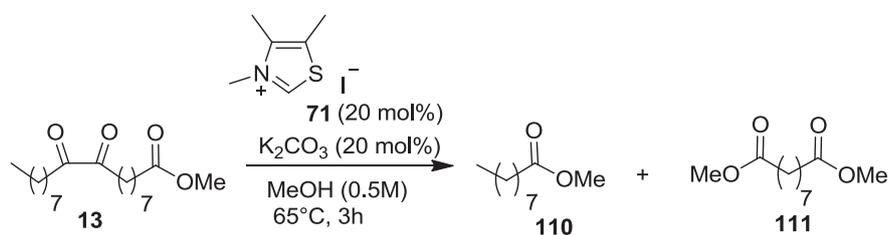
Moreover, this hypothesis is confirmed by a report of Massi *et al.*²⁹⁹ In the presence of thiamine-based catalyst, the α -diketone was considered as a acyl anion equivalent that prefers to form the coupling products. Finally, the desired esters **110** and **111** were obtained as major products from this cleavage reaction, with the formation of other by-products **118** and **119**. In order to obtain higher yields of the two esters, the cleavage of **118** and **119** to smaller products should be studied. According to Connon, in the presence of excess base and methanol, the cleavage of **118** to yield ester **110** and α -hydroxyketone **12** *via* hemiacetal **120** is conceivable (Scheme 116).²⁹⁷ Moreover, the α -ketol **12** could be also oxidized in the presence of oxygen and base to give the corresponding fatty diketone **13**.



Scheme 116: Cleavage of **118** in the presence of excess base and methanol

The investigation was first carried out in the presence of thiazolium catalyst **71** (20 mol%), K_2CO_3 (20 mol%) in methanol at 65°C for 3 hours (Table 19). The yield of two corresponding diesters **110** and **111** was determined by GC titration curves, using *n*-hexanodecane as an internal standard. The influence of oxidants was first studied in oxygen, air or argon atmosphere.

Table 19 : Influence of atmospheric condition for cleavage of diketone^[a]



Entry	Atmosphere	Conversion (%) ^b	Yield of 110 (%) ^b	Yield of 111 (%) ^b
1	O ₂	99	35	33
2 ^c	O ₂	99	38	39
3	Air	99	33	25
4	Argon	15	-	-

a) Conditions: the reaction was performed in a 25-mL schlenk, diketone (0.5 mmol), thiazolium salt **71**(20 mol%), K_2CO_3 (20 mol%), MeOH (0.5M), 65°C, 3h; b) conversion and GC yield of products were determined by GC titration; c) 100 mol% of K_2CO_3 was used.

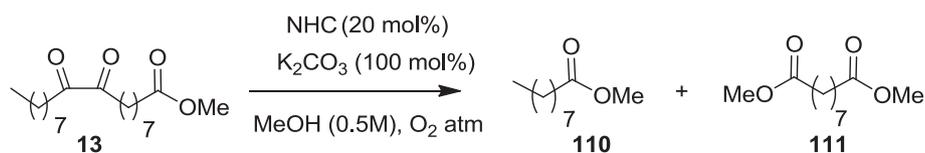
²⁹⁹ O. Bortolini, G. Fantin, M. Fogagnolo, P. P. Giovannini, V. Venturi, S. Pacifico, A. Massi, *Tetrahedron*. **2011**, *67*, 8110-8115.

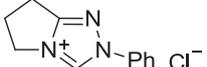
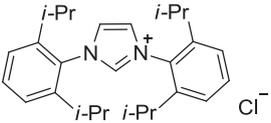
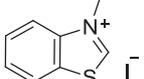
CHAPTER IV: CLEAVAGE OF DIKETONE TO ESTERS

Under oxygen (1 atm), the conversion of diketone **13** was almost complete and the esters **110** and **111** were obtained with 35% and 33% GC yield, respectively (Table 19, entry 1). Slightly improved results were also obtained when the reaction was carried out in the presence of 100 mol% of the base (Table 19, entry 2). This improvement could be explained the absence of the generation of heavier by-products **118** and **119** in GC chromatogram. Moreover, a decreasing yield of the two methyl esters was observed when air is used to replace the oxygen (Table 19, entry 3). Finally, only 15% conversion of diketone was observed and no desired products was detected when the reaction was conducted under argon atmosphere (Table 19, entry 4), demonstrating the important role of oxygen for this oxidative process. As a result, 100% mol of K_2CO_3 and atmospheric oxygen were kept for further optimization.

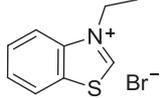
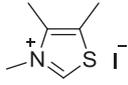
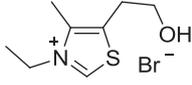
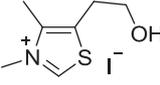
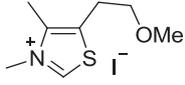
A range of commercially available azolium salts were next screened as the precatalysts for the oxidative cleavage of 1,2-diketones under typical conditions (20 mol% of azolium salt, 100 mol% of K_2CO_3) (Table 20). Triazolium **95**, imidazolium **121** and benzothiazolium **122-123** were first investigated and they all gave a full conversion (Table 20, entries 1-4). However, none of these catalysts could lead to the generation of the desired esters with significant yields. On the contrary, only thiazolium salts **69-71** could efficiently catalyze the cleavage reaction. The best result was achieved with thiamine-based catalyst **70**, providing a quantitative conversion and 42% yield of two esters **110** and **111**. Moreover, the thiazolium salt **70** has a free OH that could be oxidized during oxidation process. In order to avoid this phenomenon, the thiazolium salt **124** with *O*-methyl protection was synthesized and evaluated under these conditions. However, no better results were obtained with precatalyst **124**. Finally, thiazolium salt **70** was selected for further optimization.

Table 20 : Screening the nature of the precatalysts for oxidative cleavage of diketone



Entry	NHC precatalysts	Conversion (%) ^b	Yield of 110 (%) ^b	Yield of 111 (%) ^b	
1		95	99	7	11
2		121	99	6	3
3		122	99	6	5

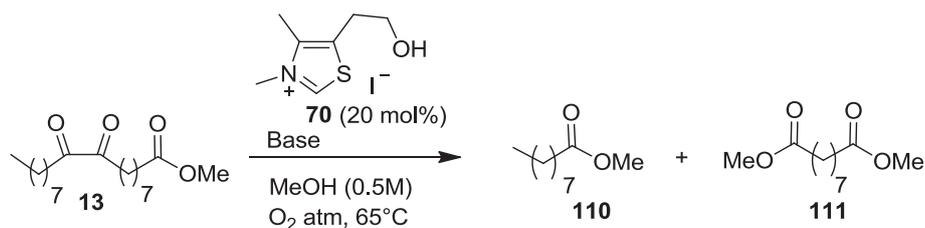
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4		123	98	7	6
5		71	98	38	39
6		69	94	39	31
7		70	99	42	42
8		124	99	40	36

a) Conditions: the reaction was performed in a 25-mL schlenk, diketone **13** (0.5 mmol), NHC (20 mol%), K_2CO_3 (100 mol%), MeOH (0.5M), 65°C, 3h; b) conversion and GC yield of products were determined by GC titration.

The nature of the base and the base loading were next investigated, using thiazolium salt **70** as the precatalyst under oxygen (ballon) in MeOH (0.5M) at 65°C (Table 21). Among all organic based tested, only DIPEA provided satisfactory results with 28 and 37% yield for the desired esters **110** and **111** (Table 21, entry 3). All inorganic bases (AcOK, *t*-BuOK, K_2CO_3) gave a full conversion (Table 21, entries 4-6) but only K_2CO_3 gave a moderate yield (42%) of each esters (Table 21, entry 6). Moreover, increasing the base loading to 200% and 300% did not allow to improve these results (Table 21, entries 7-8).

Table 21: Influence of base and base loading for oxidative cleavage of diketone^[a]



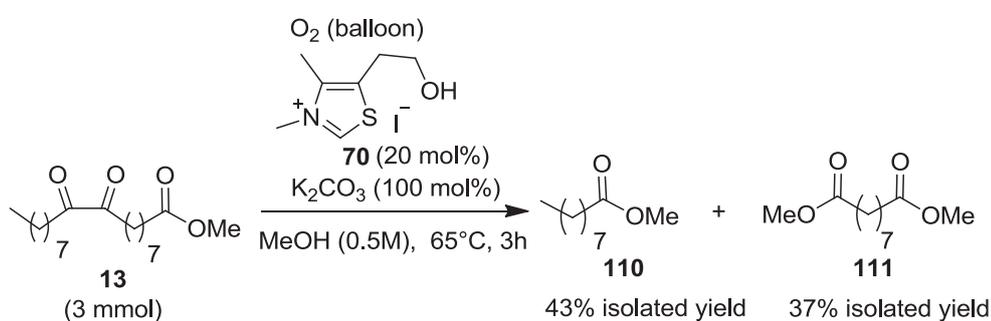
Entry	Base	Base loading (mol%)	Conversion (%) ^b	Yield of 110 (%) ^b	Yield of 111 (%) ^b
1	DBU	100	97	16	22
2	Et ₃ N	100	78	9	12
3	DIPEA	100	98	28	37
4	<i>t</i> -BuOK	100	99	13	12
5	AcOK	100	95	10	18

CHAPTER IV: CLEAVAGE OF DIKETONE TO ESTERS

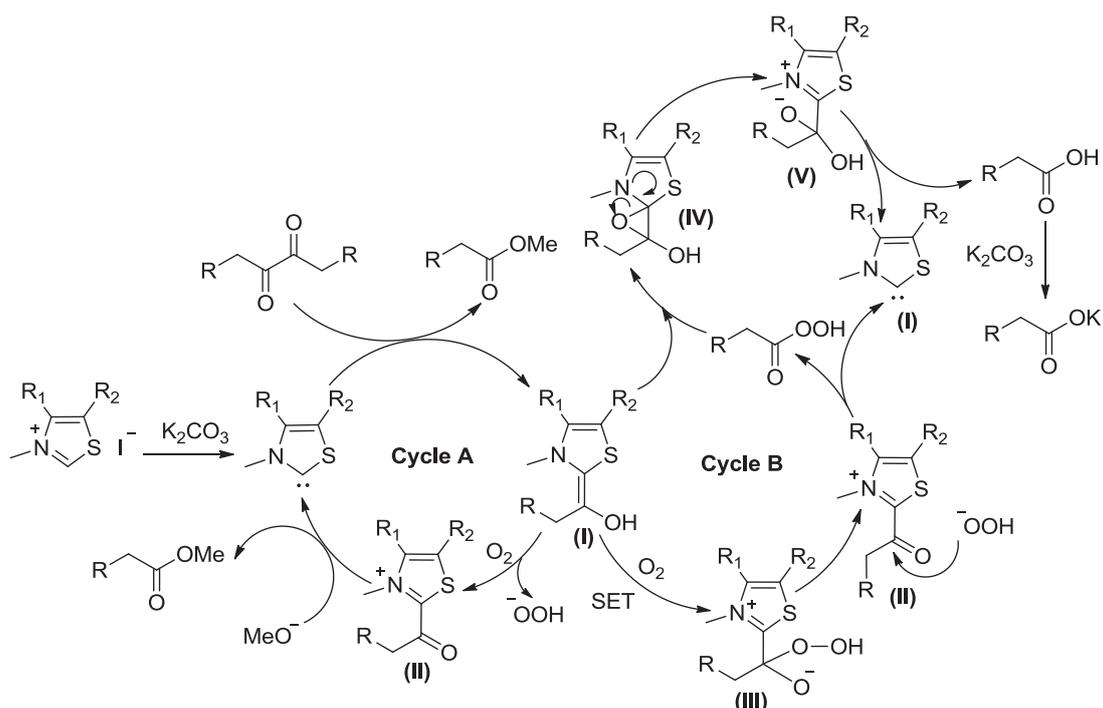
6	K ₂ CO ₃	100	99	42	42
7	K ₂ CO ₃	200	99	17	13
8	K ₂ CO ₃	300	99	12	15

^aConditions: the reaction was performed in a 25-mL schlenk, diketone **13** (0.5 mmol), thiazolium salt **70** (20 mol%), K₂CO₃ (100 mol%), MeOH (0.5M), 65°C, 3h; ^b conversion and GC yield of products were determined by GC titration.

After optimization, the conversion was also complete for almost all cases and the maximum yield for each ester reached a plateau at 42%. To confirm this result, the reaction was scaled-up using 1 g of diketone **13** derived from methyl oleate (3 mmol). The isolated yield of **110** and **111** were observed in 43% and 37% respectively, confirming the previous result of GC yield (Scheme 117).



Based on our observation, other species, representing half of the cleavage, must be generated during the reaction. Moreover, these species are not detected by GC or GC-MS. Otherwise, it should be noted that a slightly excess of the base (K₂CO₃) is required to afford the highest yield of the esters. So, we hypothesized that the corresponding potassium carboxylates were formed as the major by-products. Indeed, from a mechanism point of view, the Breslow intermediate was generated after releasing the first ester, then there are two pathways for the oxidative step (Scheme 118). The first route (cycle A) involves the oxidation of Breslow intermediate (I), to form an acyl thiazolium species (II) that could be converted to the second ester *via* nucleophilic addition of alcoholate species. The second route (cycle B) is related with single electron transfer (SET) that a Breslow intermediate was oxidized in the presence of oxygen to the intermediate (III). Then, this species could be converted to the acyl thiazolium (II) and hydroperoxide species. This compound could oxidize another Breslow intermediate to give an unstable spiro-epoxide (IV) and the corresponding carboxylic acid. Then, the opening of the epoxide could generate intermediate (V) that finally produces the desired carboxylic acid and free carbene.

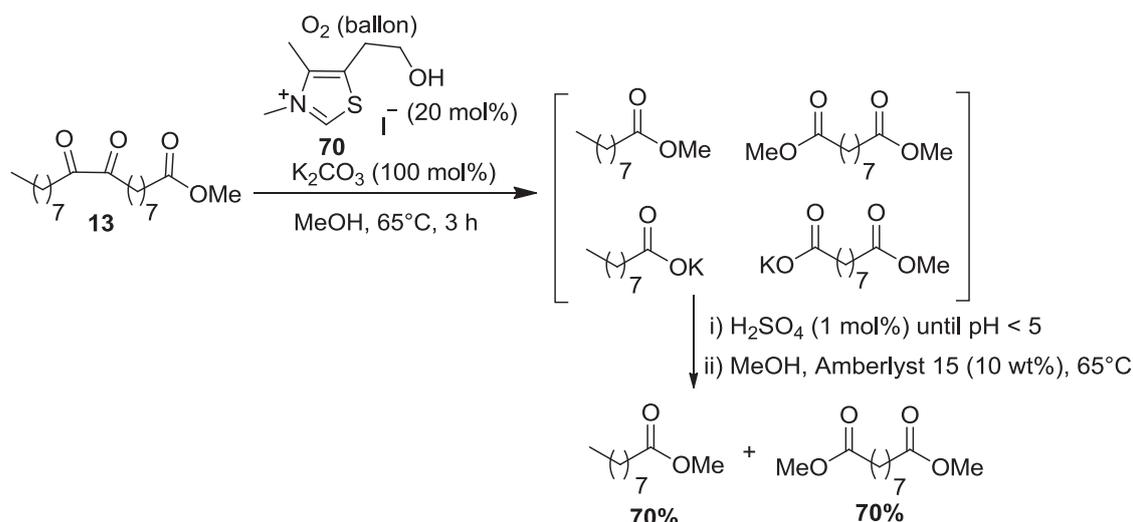


Scheme 118: Proposal mechanism for the formation of carboxylate

Under our conditions, the carboxylic acid could be trapped as a potassium carboxylate. This is in accordance with our experimental results, showing that an excess of base is necessary to afford good yields (Table 21). A mixture of carboxylic acid and corresponding ester was observed as the products of the cleavage of aromatic diketone.

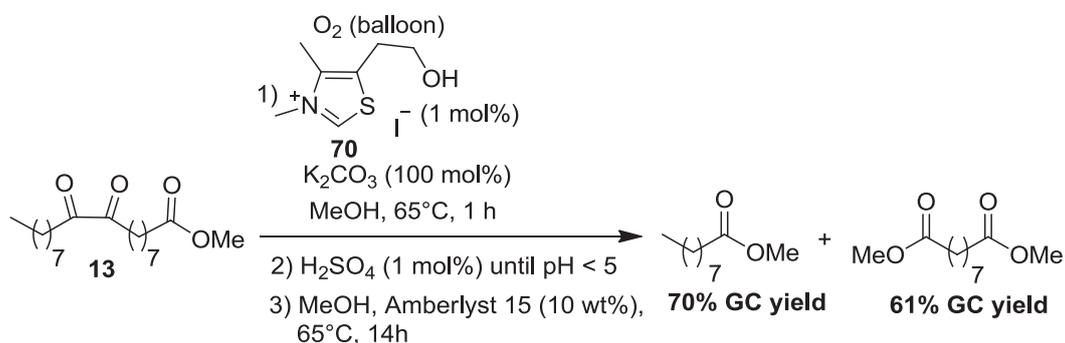
To evaluate this hypothesis, the cleavage reaction of 1,2-diketone **13** was carried out under optimized conditions (20 mol% thiazolium salt **70**, 100 mol% K_2CO_3 , oxygen atmospheric, $65^\circ C$) but the work-up was modified (Scheme 119). An acid treatment until $pH < 5$ was employed, followed by esterification with an excess of methanol in the presence of Amberlyst-15. This procedure allows the formation of two desired esters as the only products as confirmed by GC chromatogram of the crude after the treatment. Finally, the products were purified by column chromatography to give each esters **110** and **111** with 70% isolated yield. Recently, this hypothesis was also confirmed by a study of Bortolini who has reported the oxidative pathway of Breslow intermediate.³⁰⁰

³⁰⁰ O. Bortolini, C. Chiappe, M. Fogagnolo, A. Massi, C. S. Pomelli, *J. Org. Chem.* **2017**, *82*, 302–312.



Scheme 119: Oxidative cleavage of a fatty diketone-1,2 under optimized conditions

A further investigation was attempted to decrease the catalyst loading of the thiazolium salt **70**. The reaction was carried out in the presence of 1 mol% precatalyst **70** in 1 hour, following by acid treatment and Fischer esterification. Surprisingly, the conversion of the fatty diketone was still complete and methyl nonanoate **110** and dimethyl azelaate **111** were obtained with a GC yield of 70% and 61%, respectively (Scheme 120).



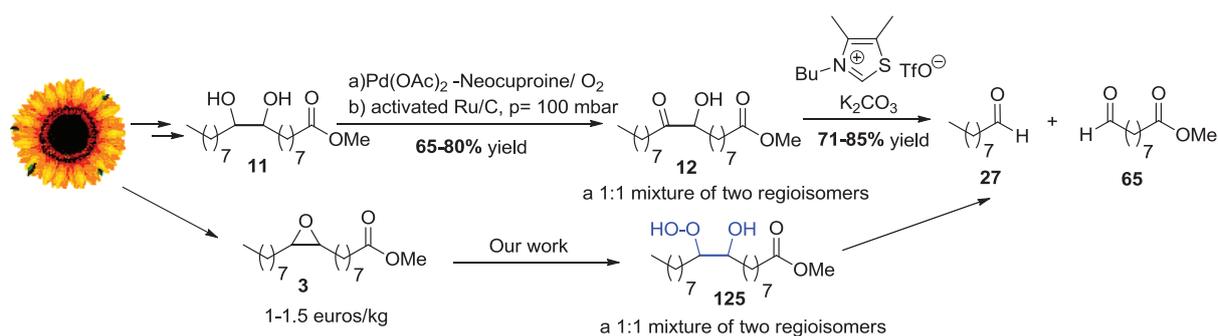
Scheme 120: NHC-mediated cleavage of fatty diketones to corresponding esters

4. Conclusions

Herein, we have demonstrated that fatty 1,2-diketone **13** could be cleaved in the presence of azolium salts under oxidative conditions into two corresponding esters. It has been shown that only thiazolium salts could efficiently catalyzed this transformation and a maximum yield of 42% could be obtained for both esters. We have proven that the oxidative cleavage of vicinal diketone leads to the formation of a mixture of ester and potassium carboxylate. The carboxylate present in this mixture could be easily converted into the desired esters by an acidic treatment to give a 70% overall isolated yield. The efficacy of this reaction at a low catalyst loading (1 mol%) and a short reaction time (1 hour) make this oxidative cleavage an interesting tool to convert diketone **13** to valuable products. Finally, one could imagine that the protocol could be easily applied to other fatty diketones derived from other fatty acids.

1. Introduction

In the previous part, we have described an organocatalytic cleavage of fatty α -hydroxyketones to bio-based aldehydes with good yields, up to 98% yield. Even if each step has a high conversion and selectivity, some drawbacks still remain such as the high price of triflate counter-anion sources in the optimized thiazolium salts or the preparation of α -hydroxyketones in large scale. In order to circumvent these critical issues, an alternative pathway has been developed, *via* the fragmentation of β -hydroxy hydroperoxide **125** (Scheme 121), that is easily prepared from cheap and widely available feedstocks such as epoxidized vegetable oil derivatives.



Scheme 121: An alternative pathway to synthesis of bio-aldehydes through decomposition of fatty β -hydroxy hydroperoxides

2. Literature

2.1 β -hydroxy hydroperoxides in natural products

β -hydroxy hydroperoxides are interesting chemical platforms in organic synthesis because they are considered as key precursors for the preparation of 1,2,4-trioxane derivatives, which display a precious anti-malarial activity.³⁰¹ For example, Artemisinin and its semi-synthesis derivatives, *i.e.* sesquiterpene lactones containing unusual *endo*-peroxide bridge, are considered as a standard worldwide treatment for malarial disease (Figure 16).³⁰² They were first discovered by Chinese scientist Tu Youyou in 1972 and were isolated from Chinese plant *Artemisia annua*. This discovery was also brought a half of Nobel Prize in Medicine 2015 for Professor Tu Youyou.³⁰³ Moreover, these 1,2,4-trioxane derivatives have exhibited some biological activities such as antitumor,³⁰⁴ antituberculosis,³⁰⁵ etc.

³⁰¹ C. Sing, H. Malik, S. K. Puri, *J. Med. Chem.* **2006**, *49*, 2794–2803.

³⁰² Y. Li, H. D. Hao, S. Wittlin, Y. K. Wu, *Chem. Asian J.* **2012**, *7*, 1881–1886.

³⁰³ <https://www.nobelprize.org/prizes/medicine/2015/tu/facts/>, retrieved in July 2018.

³⁰⁴ N. Terzić, D. Opsenica, D. Milić, B. Tinant, K. S. Smith, W. K. Milhous, B. A. Šolaja, *J. Med. Chem.* **2007**, *50*, 5118–5127.

³⁰⁵ B. A. Šolaja, N. Terzić, G. Pocsfalvi, L. Gerena, B. Tinant, D. Opsenica, W. K. Milhous, *J. Med. Chem.* **2002**, *45*, 3331–3336.

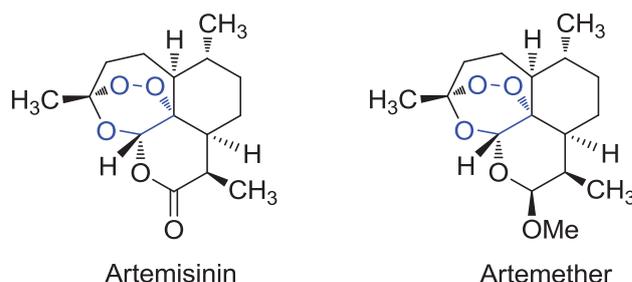
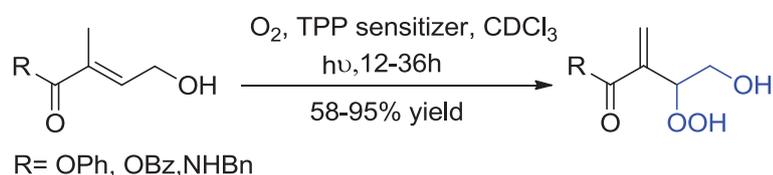


Figure 16: Artemisinin and its semi-synthetic derivatives for the treatment of malarial disease

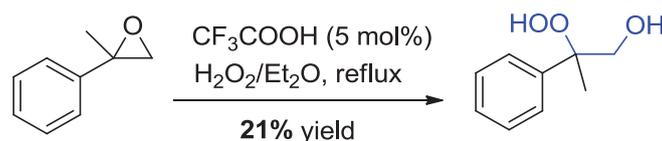
2.2 The synthesis of β -hydroxy hydroperoxides

The synthesis of β -hydroxy hydroperoxides is quite underexploited. Until now, there are two main pathways to approach these intermediates. The first route involves the oxidation of allylic alcohol (Scheme 122).³⁰⁶⁻³⁰⁷ Even if this method gave a good yield of the desired products, this photooxygenative pathway suffers from the access of the substrates.



Scheme 122: Photooxygenation of allylic alcohols to access β -hydroxy hydroperoxides

The second pathway is related to the ring-opening of epoxides with hydrogen peroxide. Initially, this reaction was carried out in the presence of strong acids such as HClO_4 ³⁰⁸ or CF_3COOH (Scheme 123).³⁰⁹ However, this reaction gives low yields of the peroxide products and suffers from the use of ethereal solution that is quite explosive and dangerous. Moreover, the scope is limited for to aromatic derivatives.



Scheme 123: Homogeneous acid catalyzed for ring-opening epoxides to peroxide species

Recently, some improvement methods have been reported using a certain amount of catalysts such as Na_2MoO_4 /glycine,³¹⁰ phosphotungstic acid,³¹¹ tin (IV) chloride (SnCl_4).³¹² Although these catalytic systems give good yields, up to 96% of β -hydroxy hydroperoxides, all of these methods suffer from the requirement of a metal catalyst (Mo, W and Sn-based catalyst) and have been performed under homogeneous condition, leading to a difficult separation and recycling of the

³⁰⁶ A. G. Griesbeck, V. Schlundt, J. M. Neudörfel, *RSC Adv.* **2013**, *3*, 7265-7270.

³⁰⁷ C. Singh, H. Malik, *Org. Lett.* **2005**, *7*, 5673-5676.

³⁰⁸ V. Subramanyam, C. L. Brizuela, A. H. Soloway, *J. Chem. Soc. Chem. Commun.* **1976**, 508-509.

³⁰⁹ Y. Ogata, Y. Sawaki, H. Shimizu, *J. Org. Chem.* **1978**, *43*, 1760-1763.

³¹⁰ W.-B. Han, Y. Wu, *Org. Lett.* **2014**, *16*, 5706-5709.

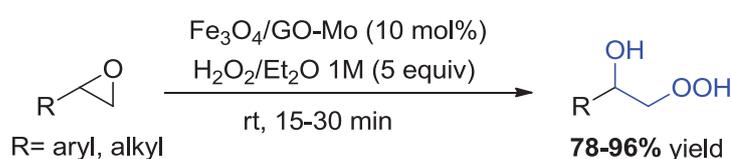
³¹¹ Y. Li, H. D. Hao, Y. K. Wu, *Org. Lett.* **2009**, *11*, 2691-2694.

³¹² X. Yan, C. H. Qiao, Z. W. Guo, *Synlett* **2013**, 502-506.

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catalysts. Moreover, the scope for this transformation is quite limited. Only examples for aromatic and short-chain terminal epoxides are given and unactivated fatty epoxides are not tested under these conditions.

To avoid the drawbacks of homogeneous reaction, some heterogeneous catalysts have been used *e.g.* $\text{SbCl}_3/\text{SiO}_2$,³¹³ phosphomolybdates/NPs CoFe_2O_4 ³¹⁴ or Molybdenum/Graphene oxide³¹⁵ and gave a yield up to 96% for aromatic epoxides (Scheme 124). Moreover, these catalysts could be reused at least 5 times without losing activity. However, some of above approaches have certain shortcomings such as the leaching of metal species, the use of expensive catalyst or the use of explosive reagent (an ethereal solution of H_2O_2). In this context, more eco-friendly method for ring-opening of epoxides is highly desirable.



Scheme 124: Synthesis of β -hydroxyperoxide alcohols in the presence of Mo-heterogenized catalyst

Although the preparation of aromatic β -hydroxy hydroperoxide is known, the synthesis of fatty hydroperoxide species is quite underexplored. Up to now, based on our knowledge, there are two articles mentioning the preparation of these fatty substrates (Scheme 124). The first synthesis of oleochemical β -hydroxy hydroperoxides was reported by Hiroko *et al.* in a patent in 2002.³¹⁶ The oxidation reaction of methyl oleate was carried out at 35°C, employing tungstic acid (12 mol%) as a catalyst and hydrogen peroxide as an oxidant (Scheme 125, conditions a). After 5 hours, a full conversion of oleic acid methyl ester was observed but only 28% of fatty peroxide was obtained. The second report of fatty hydroperoxide was described by Ruffo *et al.* in 2015.³¹⁷ The oxidation of oleic acid was carried out in the presence of tungstic acid (1 mol%) and an excess of hydrogen peroxide (4 equiv) at 70°C. After 4 hours, a complete conversion of oleic acid was obtained. However, the selectivity of the desired product was approximately 45%, due to the formation of the inevitable fatty 1,2-diol as a by-product (Scheme 125, conditions b).

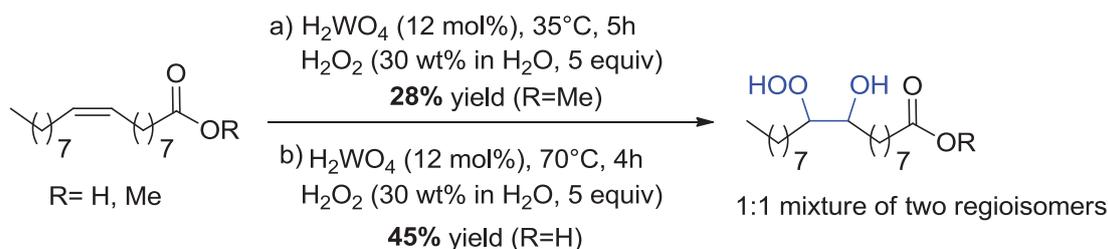
³¹³ Y. H. Liu, Z. H. Zhang, T. S. Li, *Synthesis* **2008**, 3314–3318.

³¹⁴ P.-H. Li, B.-L. Li, Z.-M. An, L.-P. Mo, Z.-S. Cui, Z.-H. Zhang, *Adv. Synth. Catal.* **2013**, 355, 2952–2959.

³¹⁵ Y.-H. Liu, H.-C. Hu, Z.-C. Ma, Y.-F. Dong, C. Wang, Y.-M. Pang, *Monatsh. Chem.* **2018**, 149, 551–556.

³¹⁶ I. Shinichiro, N. Sunao, N. Takuji, K. Hiroko, Jpn. Kokai Tokkyo Koho 2003342255.

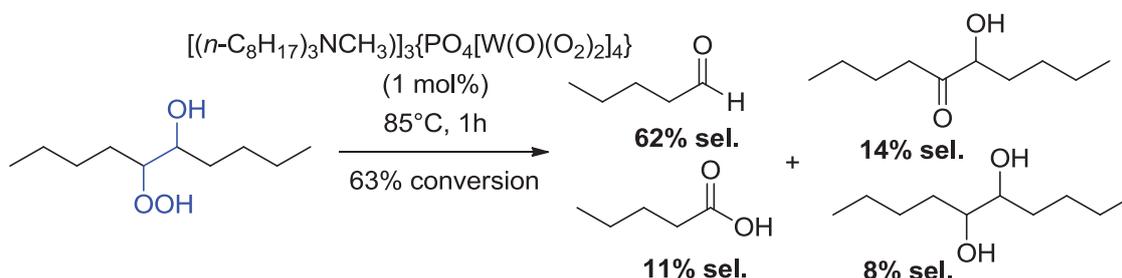
³¹⁷ V. Benessere, M. E. Cucciolito, A. De Santis, M. Di Serio, R. Esposito, F. Ruffo, R. Turco, *J. Am. Oil Chem. Soc.* **2015**, 92, 1701–1707.



Scheme 125: The preparation of fatty β -hydroxy hydroperoxide catalyzed by tungstic acid

2.3 The fragmentation of β -hydroxy hydroperoxide

Next to the synthesis of perketal or 1,2,4-trioxane, displaying a variety of biological activities, the cleavage of β -hydroxy hydroperoxides to aldehydes has also been reported. Industrially, aldehydes could be synthesized by hydroformylation of olefins¹²⁶ or by reductive ozonolysis of alkenes.¹⁸⁴ However, both methods suffer with the use of highly energy intensive process or the requirement of high purity metal-catalyst and sophisticated ligands. In the earlier work, Venturello *et al.* reported that the decomposition of aliphatic β -hydroxy hydroperoxide in the presence of quarternary ammonium dioxoperotungstate (1 mol%) at 85°C gave a good conversion (62%) after 1 hour and the desired aldehydes were obtained in 62% selectivity with the formation of the corresponding acid, diol and α -hydroxyketone in 11, 8 and 14% selectivity, respectively (Scheme 126).

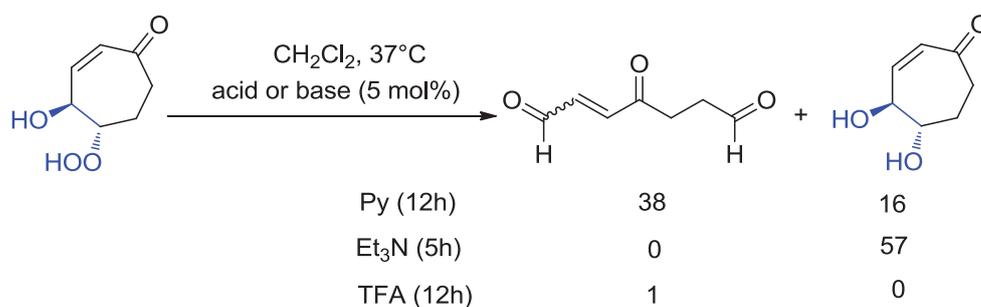


Scheme 126: Decomposition of β -hydroxy hydroperoxide in the presence of ammonium perotungstate

More recently, Salomon *et al.* investigated the cleavage of hydroperoxide species in the presence of catalytic amount of exogenous acids or bases (Scheme 127).³¹⁸ On the one hand, trifluoroacetic acid gave a quantitative conversion but a trace of desired aldehyde (1%) was obtained. On the other hand, the use of external base such as pyridine or triethylamine provided a moderate yield of free aldehyde (38%) and the corresponding diol was obtained as the major by-products (16-57%) from this transformation.

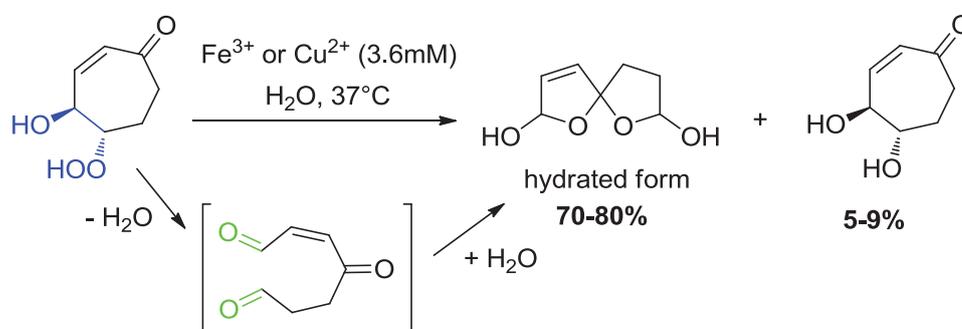
³¹⁸ X. Gu, W. Zhang, R. G. Salomon, *J. Org. Chem.* **2012**, 77, 1554–1559.

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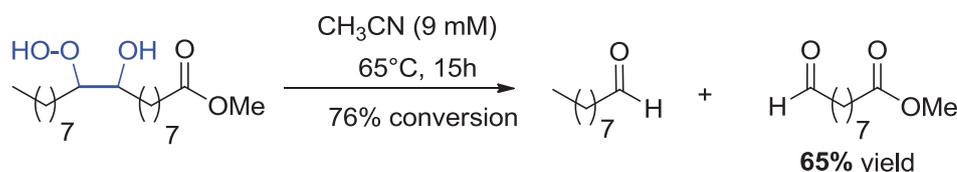
Scheme 127: Acid or base-catalyzed cleavage of hydroperoxide species to corresponding aldehyde

However, the use of metal ions as a promoter such as Fe^{3+} , Cu^{2+} or the combination of vitamin C and these cations could aid the cleavage of the peroxy species at 37°C and gives the aldehydes as hydrate form, up to 80% selectivity in a short reaction time (5-30 minutes) (Scheme 128). Besides, the corresponding diol was also obtained in 5-9% yield, due to the homolytic cleavage of hydroperoxide substrate.



Scheme 128: Metal ion-promoted decomposition of hydroperoxide species to corresponding aldehyde

Similarly, Hiroko *et al.* claimed that fatty aldehydes were obtained from the cleavage of fatty β -hydroxy hydroperoxides in 65% yield (Scheme 129).³¹⁶ However, a very low concentration of peroxide species (9 mM) and a low yield (28%) in the preparation of β -hydroxy hydroperoxide limit the application of this method.

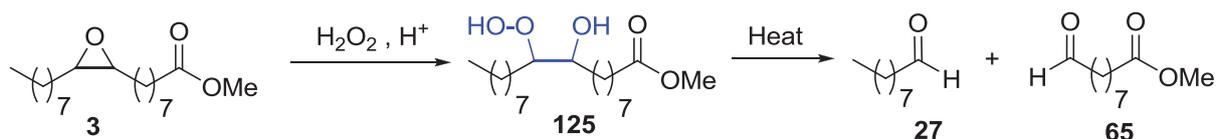


Scheme 129: Catalyst-free cleavage of peroxide species to bio-fatty aldehydes

Herein, we have summarized almost all of the pathways to synthesize β -hydroxy hydroperoxides as well as to decompose them to corresponding aldehydes. However, most of them suffer from the use of dangerous agent (ethereal solution of hydrogen peroxide) or requirement an excess of solvent and long reaction time. Then, a eco-friendly method with good yields of both fatty β -hydroxy hydroperoxide and aliphatic aldehydes are highly desirable.

3. Results and discussions

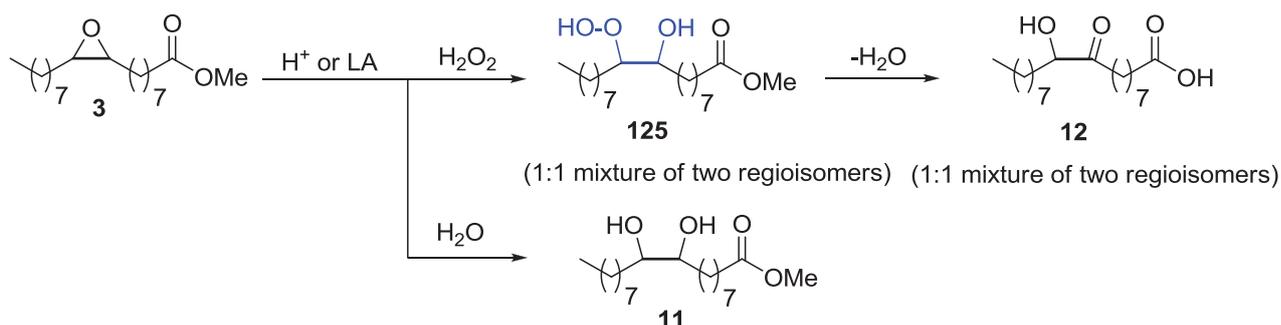
In this context, we have studied the preparation of bio-aldehydes from unsaturated fatty acid derivatives through a two-step synthesis (Scheme 130). The first step is the preparation of fatty β -hydroperoxide in the presence of acid catalyst and hydrogen peroxide (in H_2O). Unlike the traditional works using oleic acid or methyl oleate,^{316,317} epoxidized methyl oleate was selected as a model substrate, due to its cheap price and widely availability (1-1.5 eur/kg). The second step involves the decomposition of peroxide species in the presence of catalyst in various solvents and temperatures.



Scheme 130: The preparation of β -hydroxyperoxide alcohols to approach bio-aldehydes

3.1 The preparation of the fatty β -hydroxy hydroperoxides

The ring-opening of fatty oxirane was first carried out in the presence of acid catalyst (5 mol%) in *t*-BuOH at 50°C, using hydrogen peroxide as an oxidant. Firstly, a range of catalysts was screened to find the best catalyst for this transformation. After 1 hour, β -hydroxy hydroperoxide **125** and the fatty diol **11** were detected as the major products (Scheme 131). On the one hand, β -hydroxy hydroperoxide **125** was formed *via* nucleophilic addition of hydrogen peroxide onto fatty epoxide **3**. On the other hand, the vicinal diol **11** was generated by ring-opening of epoxidized oleic acid methyl ester in the presence of acid and water (from the hydrogen peroxide solution). A small amount of the corresponding α -hydroxyketone **12** was also detected as a by-product from degradation of β -hydroxy hydroperoxide **125** (Scheme 131).



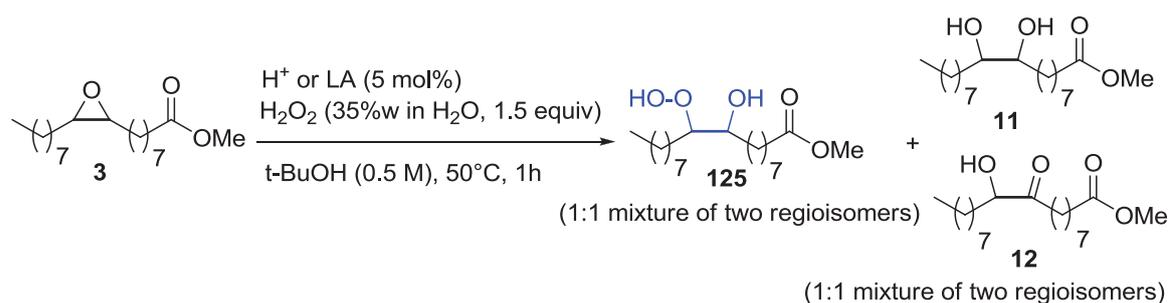
Scheme 131: Potential products from the ring-opening of fatty epoxide in the presence of H_2O_2

First, paratoluene-sulfonic acid (PTSA) was used as a catalyst for this model reaction. After 1 hour, 70% conversion of the fatty epoxide was obtained but the corresponding diol **11** was observed as the major product in 85% selectivity, due to the high acidity of PTSA (Table 22, entry 1). Then, Montmorillonite-KSF and K-10 were next investigated under standard conditions. Only 6% conversion was observed with Montmorillonite K-10 (Table 22, entry 2). However, a good conversion (92%) and 85% selectivity of fatty diol **11** were observed when Montmorillonite KSF was used (Table 22, entry 3). In fact, a difference in the conversion could be explained by the

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acidity of the solid Lewis acid. Since Montmorillonite K-10 (pKa =3-4) was employed, this catalyst was not enough acidic to activate the oxirane ring. However, when Montmorillonite KSF, with a pKa of approximately 2, was used, the reaction occurred smoothly but with a low selectivity for the desired product **125**. Then, a phosphomolybdic acid ($\text{H}_3\text{PO}_4 \cdot 12\text{MoO}_3$) was also probed under standard conditions. After 1 hour, 95% conversion and 52% selectivity for the desired product were obtained (Table 22, entry 4). An improved result was observed when phosphotungstic acid ($\text{H}_3\text{PO}_4 \cdot 12\text{WO}_3$) was tested for this model reaction. After 1 hour, a quantitative conversion of epoxidized methyl oleate was observed and a good selectivity (55%) of the peroxide product was afforded, in parallel with the formation of 33% of diol **11** and 4% of α -ketol **12** (Table 22, entry 5). Then, tungstic oxide (WO_3) was next candidate for this kind of transformation. After 1 hour, an almost complete conversion (94%) with a moderate selectivity (55%) for the peroxide product **125** was reported (Table 22, entry 6). In parallel, 40% of fatty diol **11** and 5% of α -ketol **12** were generated as major un-wanted products. Phosphoric acid (85 wt% in H_2O) was also evaluated under these conditions but no conversion was obtained with this inorganic acid (Table 22, entry 7). Finally, phosphotungstic acid was chosen for further investigation.

Table 22: The screening of the catalyst for ring-opening of oxiran into peroxy species^[a]



Entry	Catalyst	Conversion (%) ^b	Selectivity of 125 (%) ^b	Selectivity of 11 (%) ^b	Selectivity of 12 (%) ^b
1	PTSA	70	12	85	3
2	Montmorillonite K10	6	4	85	1
3	Montmorillonite KSF	92	5	85	1
4	Phosphomolybdic acid $\text{H}_3\text{PO}_4 \cdot 12\text{MoO}_3$	95	52	35	3
5	Phosphotungstic acid $\text{H}_3\text{PO}_4 \cdot 12\text{WO}_3$	99	55	33	4
6	WO_3	94	55	40	4
7	H_3PO_4 (85 wt% in H_2O)	trace	-	-	-

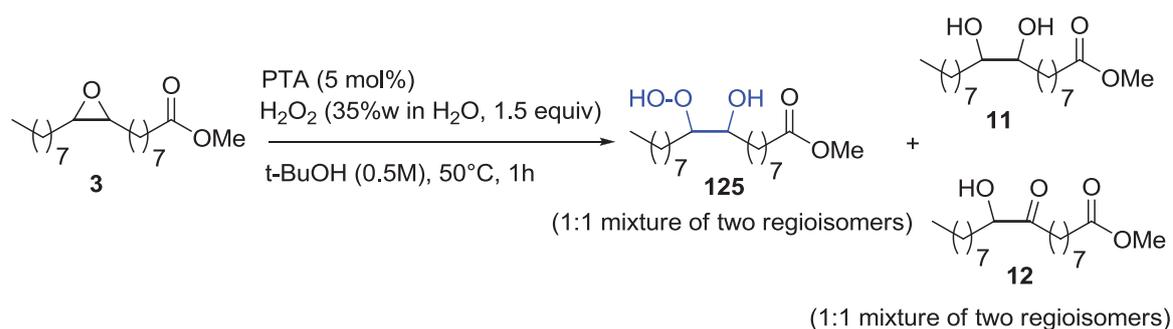
a) Conditions: the reaction was performed in a 25-mL schlenk, epoxide (1.5 mmol), acid catalyst (5 mol%), t-BuOH (0.5M), 50°C, 1h;

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b) conversion and GC yield of products were determined by GC and NMR analysis.

The concentration of the starting material **3** in *t*-BuOH was next investigated (Table 23). When a 1M concentration of epoxide **3** was used, a quantitative conversion was obtained with the formation of 55% peroxide species **125** (Table 23, entry 1). An improvement of the selectivity to 60% was obtained when a concentration of 0.5M was used (Table 23, entry 2). A further dilution (0.25M) was also tested but no more better result was observed (Table 23, entry 3). Finally, a concentration of epoxide **3** of 0.5M in *t*-BuOH was kept for further optimisation.

Table 23: Influence of concentration of fatty epoxide in solvent for model reaction^[a]



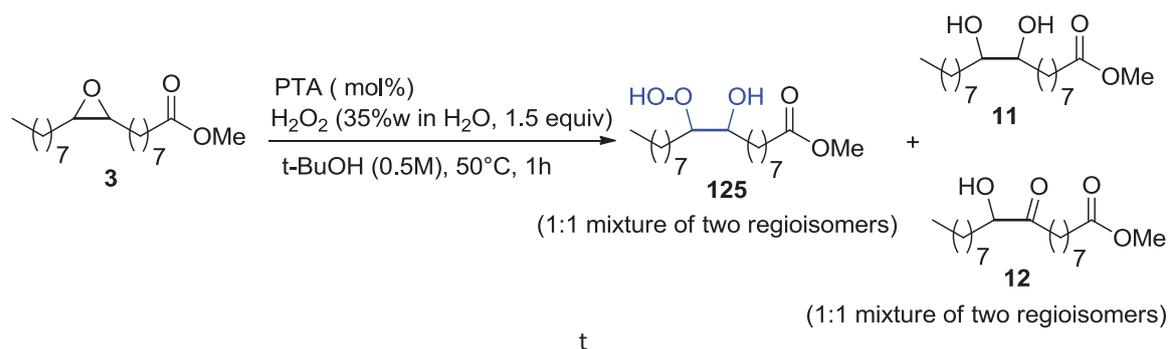
Entry	SM in <i>t</i> -BuOH (M)	Conversion (%) ^b	Selectivity of 125 (%) ^b	Selectivity of 11 (%) ^b	Selectivity of 12 (%) ^b
1	1	99	55	33	5
2	0.5	99	60	30	5
3	0.25	99	60	30	5

a) Conditions: the reaction was performed in a 25-mL schlenk, epoxide **3** (1.5 mmol), PTA (5 mol%), *t*-BuOH, 50°C, 1h; b) conversion and GC yield of products were determined by GC and NMR analysis.

The catalyst loading was next investigated under standard condition (1.5 equiv of H₂O₂, 50°C, *t*-BuOH 0.5M, 1h) (Table 24). A range of acid loading (5, 1 and 0.5 mol%) was evaluated and almost complete conversions were observed for all cases. On the one hand, 60% selectivity of desired product **125** was obtained in the presence of 5 mol% acid catalyst (Table 24, entry 1). On the other hand, a slightly better selectivity of peroxide species **125** (70%) was obtained when 1 mol% acid catalyst was used (Table 24, entry 2). A similar result was also obtained with 0.5 mol% of phosphotungstic acid but a prolonged reaction time is required for complete conversion of this reaction (Table 24, entry 3). Finally, a loading of phosphotungstic acid of 1 mol% was selected for the next investigation.

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Table 24: Screening of catalyst loading for ring-opening of fatty epoxide to peroxy species



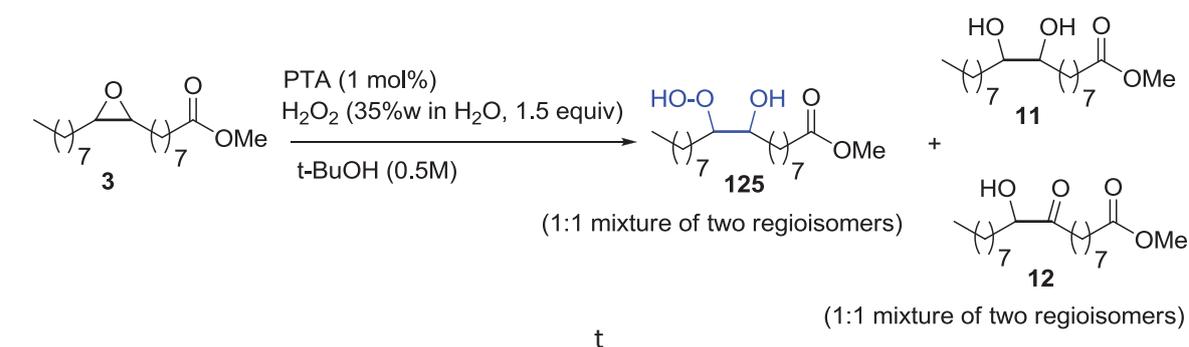
Entry	Catalyst loading (mol%)	Conversion (%) ^b	Selectivity of 125 (%) ^b	Selectivity of 11 (%) ^b	Selectivity of 12 (%) ^b
1	5	99	60	30	5
2	1	99	70	22	5
3	0.5	99	72	20	5

a) Conditions: the reaction was performed in a 25-mL schlenk, epoxide (1.5 mmol), PTA, t-BuOH (0.5M), 50°C, 1h; b) conversion and GC yield of products were determined by GC and NMR analysis.

The temperature of the reaction was next screened (Table 25). The conversion of the reaction was quantitative at 70°C after 0.7 hour and 60% selectivity of peroxy species **125** was also observed (Table 25, entry 1). An lower temperature (50°C) provided a similar result (99% conversion, 70% selectivity) in a shorter reaction time (Table 25, entry 2). The reaction at 30°C gave the same result than the reaction at 50°C (Table 25, entry 3). However, reaction time should be extended (10 hours) to complete the reaction. Finally, the temperature was kepted at 50°C for next optimization.

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Table 25: Influence of the temperature for ring-opening of fatty epoxide into peroxy species^[a]



Entry	Temperature (°C)	Time (h)	Conversion (%) ^b	Selectivity of 125 (%) ^b	Selectivity of 11 (%) ^b	Selectivity of 12 (%) ^b
1	70	0.7	99	60	30	5
2	50	1	99	70	22	5
3	30	10	99	72	20	5

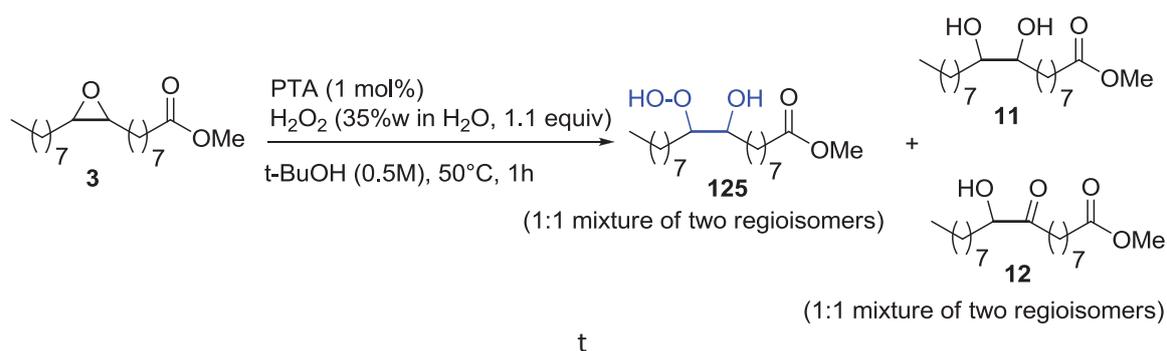
a) Conditions: the reaction was performed in a 25-mL schlenk, epoxide (1.5 mmol), PTA (1 mol%), t-BuOH (0.5M); b) conversion and selectivity of products were determined by GC and NMR analysis.

In order to diminish the formation of fatty diol **11** as the major by-product, several strategies were attempted such as using a water scavenger (to trap water from the solution of hydrogen peroxide) or using an alternative oxidant that contains less water (Table 26). First of all, some water scavengers were employed under the standard conditions (1 mol% PTA, 50°C, t-BuOH, 1h). When anhydrous sodium sulfate and 4Å molecular sieves were used, almost no conversion of the epoxide **3** was obtained, probably due to the degradation of the hydrogen peroxide solution (Table 26, entries 1-2). When anhydrous MgSO₄ was employed as the drying agent, an improved result was obtained. In the presence of 1 equivalent of MgSO₄, 80% selectivity of **125** and 16% selectivity of fatty diol **11** were obtained (Table 26, entry 3). Increasing the amount of MgSO₄ (3 equiv) provided similar results in selectivity for peroxide **125** and diol **11** with 81% and 14% respectively (Table 26, entry 4). Then, trimethyl orthoformate was also evaluated. Under these conditions, a full conversion was obtained with a declined formation of the diol **11** (10%). However, an increasing generation of α-ketol **12** (13%) led to decrease the selectivity of the peroxide **125** from 81% to 72% (Table 26, entry 6).

Actually, diol **11** is the major by-product from this transformation, due to the presence of water from the hydrogen peroxide solution. Then, an alternative oxidant containing less water was next probed for the ring-opening of fatty oxiranes. A similar result (99% conversion, 81% selectivity) was observed when a solution of hydrogen peroxide (50 %w in H₂O) was used (Table 26, entry 5). Moreover, Urea hydrogen peroxide (UHP, H₂O₂ · NH₂CONH₂) was also tested but only a trace of conversion was obtained (Table 26, entry 7), probably due to the intermolecular hydrogen bond in UHP, leading a decrease of nucleophile of hydrogen peroxide.

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Table 26: The screening of water scavenger and oxidant for this model reaction^[a]



Entry	Water scavenger (equiv)	Conversion (%) ^b	Selectivity of 125 (%) ^b	Selectivity of 11 (%) ^b	Selectivity of 12 (%) ^b
1	MS 4Å	trace	-	-	-
2	Na ₂ SO ₄ (1 equiv)	trace	-	-	-
3	MgSO ₄ (1 equiv)	99	80	16	4
4	MgSO ₄ (3 equiv)	99	81	14	4
5 ^c	MgSO ₄ (3 equiv)	99	81	14	4
6	CH(OMe) ₃ (3 equiv)	99	72	10	13
7 ^d	H ₂ O ₂ .NH ₂ CONH ₂	trace	-	-	-

a) Conditions: the reaction was performed in a 25-mL schlenk, epoxide **3** (1.5 mmol), PTA, t-BuOH (0.5M), 50°C, 1h; b) conversion and selectivity of products were determined by GC and NMR analysis; c) a solution of H₂O₂ (50%w in water) was used; d) a hydrogen peroxide urea was used without a drying agent.

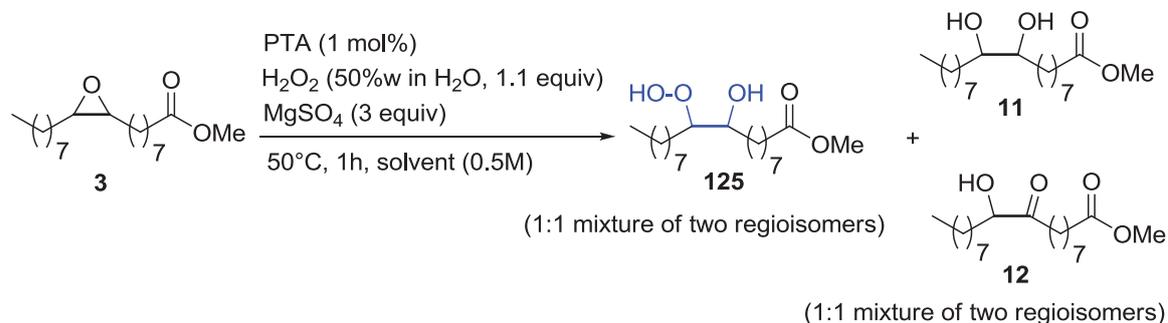
A range of various solvents was next investigated under standard condition, using phosphotungstic acid (1 mol%), MgSO₄ (3 equiv), H₂O₂ (50 wt% in H₂O, 1.1 equiv) at 50°C for 1 hour (Table 27). Tertiary alcohols such as t-BuOH, t-amyl-OH and 3-methyl-3-pentanol gave good conversions (Table 27, entries 1-3). The reaction in t-BuOH and t-amyl alcohol provided a full conversion and a high selectivity of **125** with 81 and 82% respectively (Table 27, entries 1-2). However, 3-methyl-3-pentanol gave only 70% conversion and 71% selectivity for the desire product **125** (Table 27, entry 3). On the contrary, acetonitrile provided a poor result (Table 27, entry 4), maybe caused by the degradation of hydrogen peroxide in acetonitrile in acidic medium (Radziszewski reaction).³¹⁹ Moreover, EtOAc and MTBE were also evaluated under these conditions (Table 27, entries 5-6). Although good conversions (94-99%) were obtained, a moderate selectivity of the peroxo species **125** (66-70%) were observed, indicating that both solvents are not suitable to efficiently promote the reaction. Finally, t-amyl-OH was reinvestigated but a concentration of the fatty epoxide **3** was diluted twice (0.25M) and a solution of H₂O₂ in t-amyl alcohol (0.5M) was

³¹⁹ H.-D. Brauer, B. Eilers, A. Lange, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1288–1295.

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prepared and added dropwise in reaction medium. However, a similar result (99% conversion, 81% selectivity) was observed (Table 27, entry 7) when using this protocol.

Table 27: Screening of solvent for ring-opening of epoxide to peroxy species^[a]



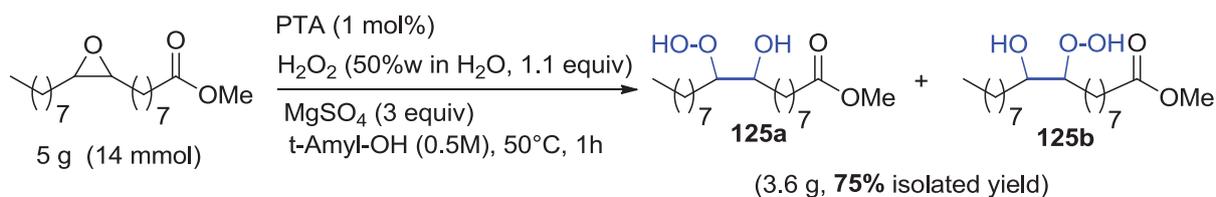
Entry	Solvent	Conversion (%) ^b	Selectivity of 125 (%) ^b	Selectivity of 11 (%) ^b	Selectivity of 12 (%) ^b
1	t-BuOH	99	81	14	4
2	t-Amyl-OH	99	82	11	4
3	3-methyl-3-pentanol	70	71	16	5
4	CH ₃ CN	-	-	-	-
5	EtOAc	94	66	15	5
6	MTBE	97	70	17	7
7 ^c	t-Amyl-OH (0.25M)	99	81	12	5

a) Conditions: the reaction was performed in a 25-mL schlenk, epoxide **3** (1.5 mmol), PTA (1 mol%), t-BuOH (0.5M); b) conversion and selectivity of products were determined by GC and NMR analysis; c) epoxide (6 mmol) was used.

Finally, in order to validate our optimization, the reaction was scaled-up under the optimized conditions using 5 g of epoxide **3** (14 mmol). The synthesis of fatty β-hydroxy hydroperoxide was conducted in the presence of phosphotungstic acid (1 mol%), MgSO₄ (3 equiv), H₂O₂ (50wt% in H₂O, 1.1 equiv) at 50°C under mechanical stirring (Scheme 132). After 1 hour, a quantitative conversion was observed and β-hydroxy hydroperoxides **125a** and **125b** were isolated in 75% yield after column chromatography as an inseparable mixture of two regioisomers.

Caution: evaporation of solutions which may contain fatty β-hydroxy hydroperoxide at a rotary evaporator represents a serious safety risk and can cause explosion and destruction of equipment. The peroxides value was 550 mmol O₂/kg (NFT 60-220).³¹⁷

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Scheme 132: Scale-up reaction for ring-opening of fatty epoxide into peroxide product

The desired products were also characterized by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ (Figure 17). The chemical shift at 11.2 ppm (s) and 4.3 ppm (dd) are characteristic for the appearance of O-OH and O-H. Moreover, a multiplet (3.6 ppm) next to a singlet of OCH_3 (3.57 ppm) confirms the presence of 2 C-H. These signals are characteristic of the β -hydroxy hydroperoxide function and this was also confirmed by $^{13}\text{C-NMR}$. Two signals at 69 and 87 ppm in $^{13}\text{C-NMR}$ are also elucidated for 2-C-H in peroxide **125**.

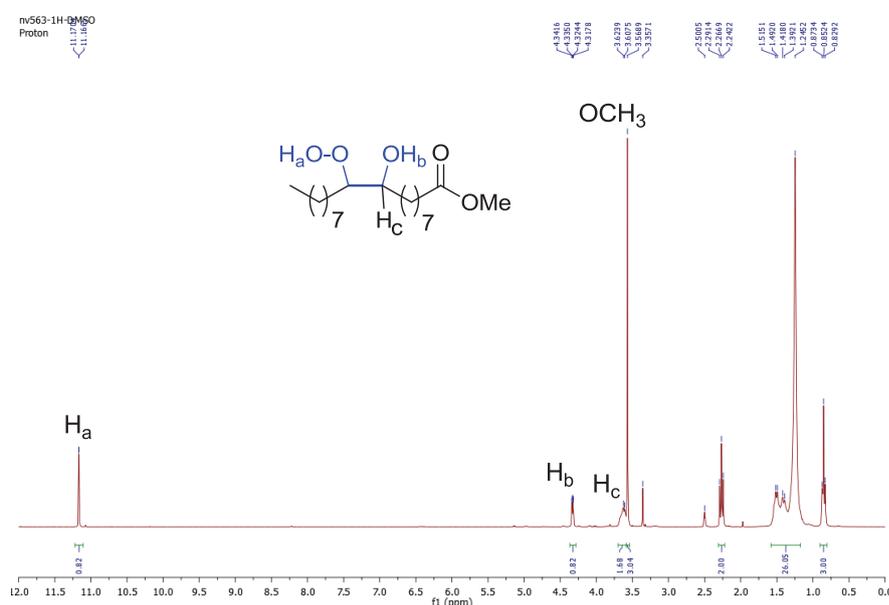


Figure 17: $^1\text{H-NMR}$ (in d_6 -DMSO, 300 MHz) of the β -hydroxy hydroperoxide **125**

When β -hydroxy hydroperoxide **125** was analysed by GC (and GC-MS), no trace of this product was detected (Figure 18). On the contrary, two aldehydes nonanal **27** and methyl azelaldehyde **65** were obtained as main products. Next to them, some α -ketol **12** and diol **11** were also observed in GC chromatography. This phenomenon could be explained by the cleavage of β -hydroxy hydroperoxide **125**. In fact, the injector temperature in the GC apparatus was approximately 300°C that was enough high to cleave the peroxide species **125** into two corresponding aldehydes.³²⁰

³²⁰ E. Antonelli, R. D'Aloisio, M. Gambaro, T. Fiorani, C. Venturello, *J. Org. Chem.* **1998**, 63, 7190-7206.

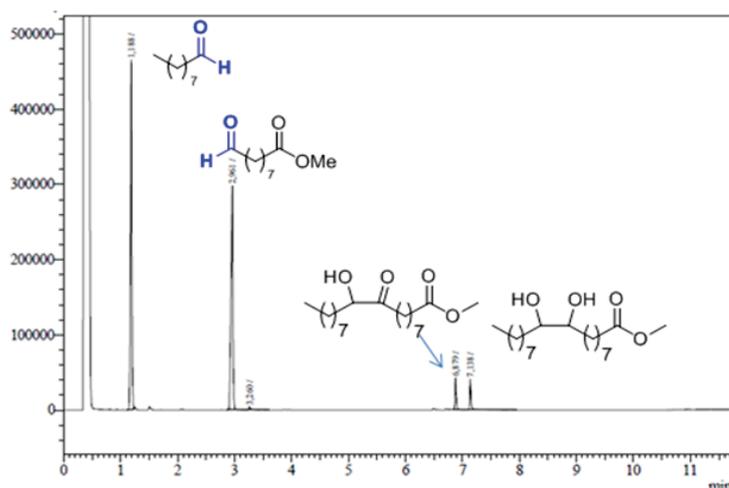


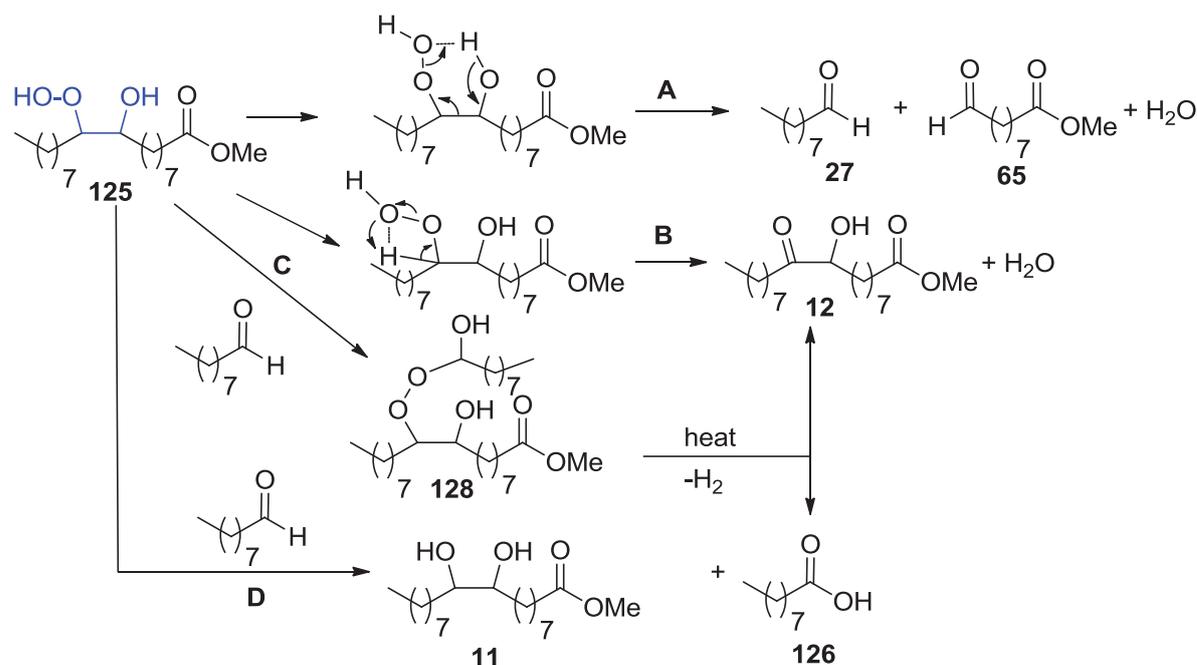
Figure 18: GC chromatography of peroxide product **125**

Consequently, we decided to take advantages of this phenomenon to develop a clean cleavage method for the synthesis of bio-aldehydes under thermal decomposition or probably under flash pyrolysis.³²¹

3.2 Cleavage of fatty β -hydroxy hydroperoxides into aldehydes

Based on our previous observation and the work of Hiroko *et al.*,³¹⁶ the cleavage of fatty β -hydroxy hydroperoxide **125** was conducted at 80°C in *tert*-amyl alcohol (0.25M).³¹⁶ After 4 hours, the quantitative conversion of **125** was obtained. However, only 45% selectivity for the aldehydes **27** and **65** was observed. The corresponding acids **126** and **127**, α -ketol **12** and diol **11** were obtained as major by-products (Scheme 133). In fact, the cleavage of β -hydroxy hydroperoxide could release the aldehydes **27** and **65** as the main pathway with water as a co-product (Scheme 133, route A). Moreover, the H of hydroperoxide species (O-OH) is quite acidic, then it could also “abstract” the C-H to give the α -ketol **12** as the major by-product (Scheme 133, route B). Furthermore, the aldehyde could react with the hydroxyperoxide species **125** to form the hemi-peracetal intermediate **128** that could be thermally decomposed to release the corresponding fatty acid and α -hydroxyketone **12** (Scheme 133, route C). On the other side, it should be noted that the aldehydes are reductants and β -hydroxy hydroperoxides are oxidants. As a result, they could also react together to provide the corresponding fatty acids and fatty diol **11** (Scheme 133, route D).

³²¹ P. J. Jones, B. Riser, J. Zhang, *J. Phys. Chem. A* **2017**, *121*, 7846-7853.

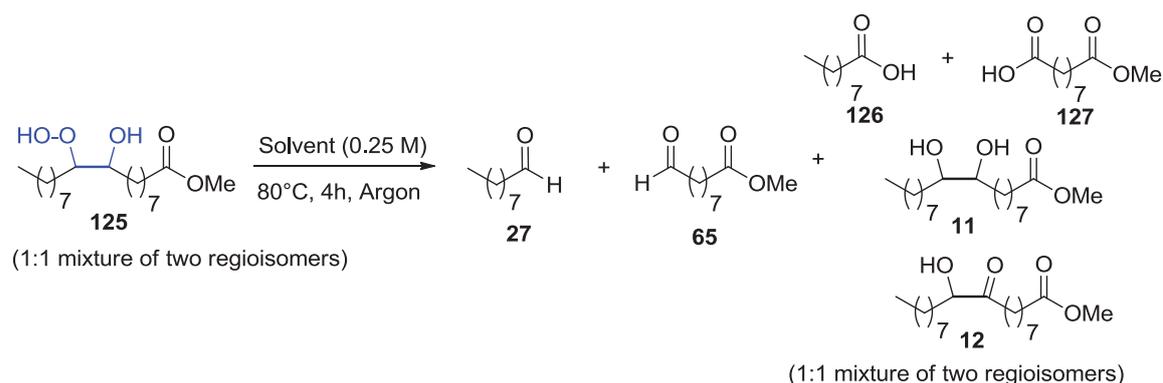


Scheme 133: Observed products from cleavage of β -hydroxy hydroperoxide **125**

Then, a range of solvents was investigated under catalyst-free conditions, using a 0.25M concentration of the peroxide **125** in solvent (Table 28). The reaction was heated at 80°C for 4 hours. Both *t*-butanol and *t*-amyl alcohol gave an excellent conversion (99%). However, only moderate selectivity of the aldehydes (44-45%) was observed (Table 28, entries 1-2). Besides the aldehydes, the reaction in tertiary alcohols promotes the formation of α -ketol **12** (12-20%) and corresponding acids **126-127** (16-27%), indicating that both of them are not good for selective cleavage of β -hydroxy hydroperoxide **125** to aldehydes. Acetonitrile was next probed for this reaction (Table 28, entry 3). After 4 hours at 80°C , the conversion of peroxide **125** was also complete but a good selectivity of 68% was obtained for the aldehydes. Otherwise, α -ketol **12**, diol **11** and the two corresponding acids **126-127** were also determined as by-products in 10, 8 and 6% selectivity, respectively. Moreover, cyclohexane and toluene were also evaluated for this cleavage reaction but messy crudes were obtained. Finally, acetonitrile was selected for the further investigation.

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Table 28: The screening of solvents for the cleavage reaction^[a]



Entry	Solvent	Conversion (%) ^b	Sel. of aldehydes (27+65) (%) ^b	Sel. of 12 (%) ^b	Sel. of 11 (%) ^b	Sel. of acids (126+127) (%) ^b
1	<i>t</i> -BuOH	99	44	20	13	12
2	<i>t</i> -amyl-OH	99	45	16	5	27
3	CH ₃ CN	99	68	10	8	6

Poor results were obtained when cyclohexane or toluene were used.

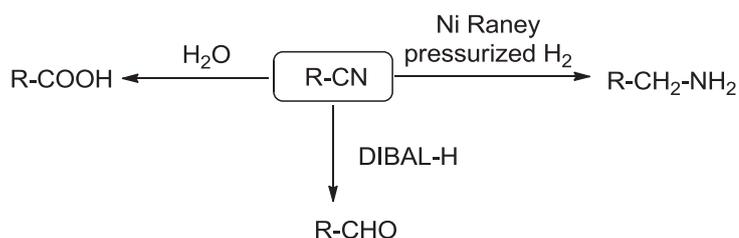
a) Conditions: the reaction was performed in a schlenk 25-mL, hydroxy hydroperoxide (0.5 mmol), solvent (2 mL, 0.25 M); b) conversion and selectivity of products were determined by GC and NMR analysis.

The temperature of the reaction was next probed. A range of temperature from 60°-100°C was employed for the cleavage reaction that was conducted in acetonitrile or propionitrile for a suitable reaction time. When the reaction was carried out in acetonitrile at 80°C, a complete conversion was obtained after 4 hours (Table 29, entry 2). However, only 68% selectivity of the aldehydes was observed. Decreasing the temperature down to 60°C gave a quantitative conversion and a slight improvement in the selectivity of aldehydes (76%) was obtained (Table 29, entry 1). However, a prolonged reaction time was required. A temperature of 100°C was also tested under these conditions. However, a boiling point of acetonitrile is approximately 80°C, then a similar solvent with higher boiling point such as propionitrile was used (Table 29, entry 3). A quantitative conversion was obtained with a selectivity of 76% for the aldehydes after a shorter time reaction (2.5 hours), indicating that propionitrile is one of the best solvents for the cleavage β-hydroxy hydroperoxide into the corresponding aldehydes.

A further attempt to improve the selectivity of the cleavage reaction was carried out, using an additive as such acid or base, or working under diluted conditions. When the reaction was performed in propionitrile (0.12 M), a same conversion was obtained after 2.5 hours (Table 29, entry 4). However, the selectivity of aldehydes was slightly dropped to 71%. On the other side, acid or base additives were also probed under these conditions. When Amberlite-15 or DBU were used, a

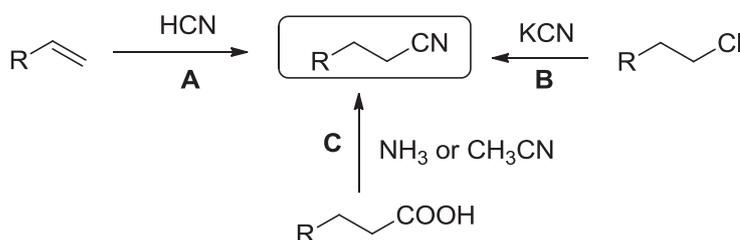
3.3 Cleavage of β -hydroxy hydroperoxides into nitriles

Fatty nitriles were also interesting chemical platforms in organic synthesis, due to their applications. First of all, nitrile derivatives could be used as key intermediates for further modifications (Scheme 134). For example, aliphatic nitrile can be hydrogenated under hydrogen pressure in the presence of metal catalyst to give fatty amines.³²² Moreover, they could be also hydrolyzed to the corresponding fatty acid or aliphatic amides.³²² Otherwise, fatty nitriles could reduce in the presence of DIBAL-H to give the imine intermediates that could hydrolyze to give the aldehydes without over-reduction.³²³ Moreover, aldehydes could be used in a wide range of applications in the preparation of polymers or surfactants.¹³



Scheme 134: Key transformations of fatty nitrile derivatives

However, based on our knowledges, there are a few pathways to access fatty nitriles (Scheme 135). The first industrial pathway involved a hydrocyanation process (Scheme 135, route A).³²⁴ For instance, adiponitrile, a key precursor in the synthesis of nylon-6,6, was prepared through hydrocyanation of 1,3-butadiene.³²⁵ The second route, known as Kolbe nitrile synthesis, relies on a metathesis reaction of an alkyl halide and a metal cyanide (Scheme 135, route B).³²⁶ However, both alkyl halide and metal cyanide are toxic and carcinogenic agents and this reaction suffers from competing selectivity between nitrile and isonitrile products. The third pathway that was recently developed, involves with the use of fatty acid derivatives and ammonium-sources (NH_3 or CH_3CN) (Scheme 135, route C).³²⁷⁻³²⁸



Scheme 135: The main pathways for preparation of fatty nitriles

³²² P. Pollak, G. Romeder, F. Hagedorn, H.-P. Gelbke, *Ullmann's Encyclopedia of Industrial Chemistry* **2002**, DOI:10.1002/14356007.a17_363.

³²³ F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, **1977**.

³²⁴ W. Tam, K. A. Kreutzer, R. J. McKinney, United States Patent N° 5688986.

³²⁵ M. T. Musser, *Ullmann's Encyclopedia of Industrial Chemistry* **2005**, DOI: 10.1002/14356007.a01_269.

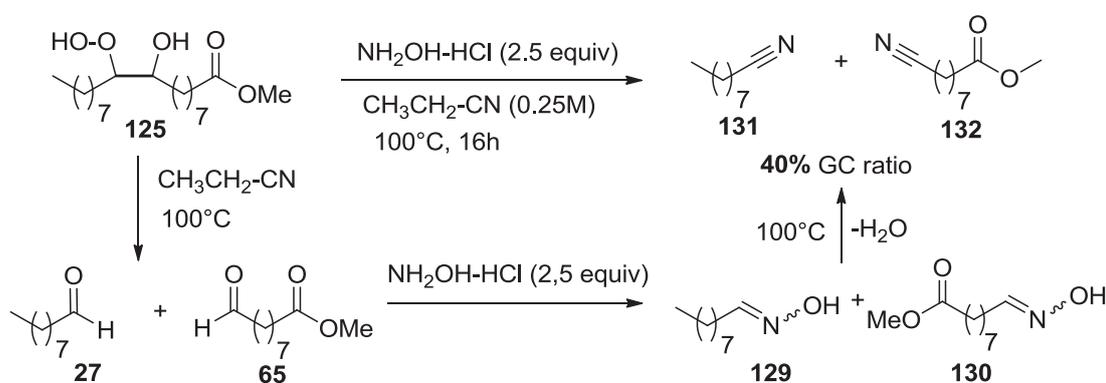
³²⁶ L. Friedman, H. Shechter, *J. Org. Chem.* **1960**, *25*, 877–879.

³²⁷ R. I. Khusnutdinov, N. A. Shchadneva, A. R. Bayguzina, Yu. Yu. Mayakova, *Russ. J. Org. Chem.* **2016**, *52*, 1282–1286.

³²⁸ M. Terasaka, T. Fukushima, United States Patent N° 20050059836.

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Because propionitrile was selected as the best solvent for the cleavage of β -hydroxy hydroperoxide **125** into the corresponding aldehydes, the cleavage of this intermediate into nitriles was conducted in propionitrile at 100°C, using hydroxylamine hydrochloride (2.5 equiv). After 16 hours, 40% GC ratio of the nitrile products **131** and **132** was determined in GC analysis. Moreover, these desired products were confirmed again by GC-MS analysis of the crude reaction mixture. In fact, this process involves to three consecutive reactions. Firstly, the aldehydes are afforded through cleavage of β -hydroxy hydroperoxide **125**. Secondly, these aldehydes are condensed with hydroxylamine to give aldoxime intermediates **129-130**. Finally, these derivatives were dehydrated under elevated temperature (100°C) to give the aliphatic nitriles **131-132** which could be further converted to value-added compounds such as fatty amines or aminoesters.

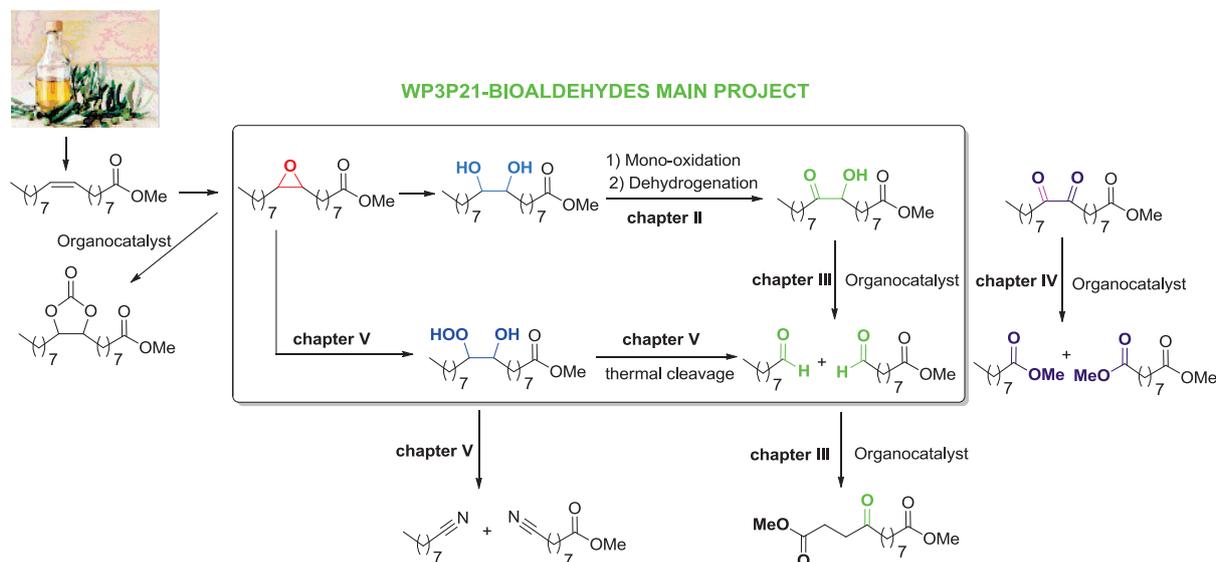


Scheme 136: Cleavage of peroxide intermediate to corresponding nitriles

Herein, we have reported a preliminary result on the cleavage of a fatty β -hydroxy hydroperoxide onto the corresponding fatty nitriles with a moderate yield (40%). A further development to optimize this cleavage method is ongoing within our laboratory.

GENERAL CONCLUSIONS AND PERSPECTIVES

During this Ph. D. work, we have developed two methods to produce bio-aldehydes from unsaturated fatty acid derivatives as well as described several valorizations of other fatty acid derivatives.



The first route involves the preparation of fatty α -hydroxyketones and their organocatalytic cleavage to give aldehydes with good yields. In this route, two conditions were developed to convert the vicinal biosourced diols to the corresponding α -hydroxyketones. The first one is the mono-oxidation of fatty diols, using a $Pd(OAc)_2$ -neocuproine complex and oxygen as an oxidant. This reaction occurs in smooth conditions, with a lot of advantages such as low catalyst loading, moderate temperature and gives a high conversion (95%) and excellent selectivity (97%) of the α -hydroxyketone derived from methyl oleate. Moreover, this catalytic system could be applied for other 10 fatty α -hydroxyketones and gave good yields (42-84%).

In order to provide a greener approach to fatty α -hydroxyketones, Ru/C was selected as the best heterogeneous metal-based catalyst for the dehydrogenation of oleochemical 1,2-diols. This process occurs at elevated temperature (175°C) under vacuum (100 mbar) to give the desired products with a high conversions and selectivity. Furthermore, the scope of this reaction was evaluated for 9 other fatty diols, including polyols derived from vegetable oil and gave good yields, up to 79%. Moreover, this heterogeneous catalyst can be recycled at least 5 times with constant and high selectivity (*ca* 90%).

The cleavage of α -hydroxyketones was studied by organocatalysis through reactive distillation. A series of thiazolium salts was synthesized and their thermal stability was evaluated by thermogravimetric analysis (TGA) to find the best catalyst for retro-benzoin condensation. Then, the retro-benzoin of fatty α -hydroxyketones was conducted at 180°C in the presence of a thermally robust thiazolium salt under reduced pressure to give aldehydes with good yields (71-85%). Moreover, these conditions could be applied to other fatty and aromatic α -hydroxyketones and gave high yield of bio-aldehydes (up to 98%).

GENERAL CONCLUSIONS AND PERSPECTIVES

In order to develop a more environmentally-friendly route to aldehydes, the preparation of fatty β -hydroxy hydroperoxides was carried out, using a cheap and renewable substrate such as epoxidized methyl oleate. The reaction was performed in the presence of phosphotungstic acid (1 mol%) at 50°C to give the desired products in 75% isolated yield. Then, the fragmentation of this species was studied under thermal condition (100°C) to provide 76% selectivity for the aldehydes. Moreover, preliminary results showed that β -hydroxy hydroperoxides could also be converted to value-added products such as fatty nitriles and fatty acids.

Next to the preparation of aldehydes, the valorization of by-products (fatty diketones) and aldehydes were also described on this manuscript. On the one hand, fatty diketones, that are the by-products from the mono-oxidation of 1,2-diols using a catalytic system of Pd(OAc)₂-neocuproine, could be cleaved into corresponding esters through organocatalysis. This reaction was carried out using thiazolium salt in the presence of oxygen (balloon), giving good yields (up to 70%) of the corresponding esters. On the other hand, aldehyde ester can be converted to 1,4-dicarbonyl derivatives (that could be used as monomers) through Stetter reaction. This reaction also occurs in the presence of a thiazolium salt and a range of Michael acceptors was also tested for this transformation, then Stetter adducts could be obtained with high yields (up to 82%).

Finally, two alternative pathways to produce fatty aldehydes from vegetable oil derivatives have been developed in this Ph. D. with several advantages such as high yields, simple conditions and relatively cheap catalysts. Even if the proof of concept has been established for these two routes, more work will be necessary to develop them on a larger scale:

- 1) For the first route, a heterogenization of thiazolium catalyst onto insoluble materials should be studied to recycle the organocatalyst. Then, a development of a continuous reactive distillation process could be investigated.
- 2) For the second pathway, a development of a continuous flow process for the preparation and cleavage of fatty β -hydroxy hydroperoxide could be investigated for the selectivity and safety reasons.

1. General information

All reagents and solvents used for synthesis were commercial and used without further purification. Methyl oleate (96% purity), technical (90% purity) oleic acid, 1-butanol, 2-ethyl hexanol, hydrogen peroxide (35% in water), nonanal (97%) were purchased from Alfa Aesar. Pd(OAc)₂, neocuproin, MeOH, *tert*-butanol and H₃PO₃ were supplied by Sigma-Aldrich and methyl 12-*O*-acyl ricinoleate (80% GC) by TCI. All catalysts such as Ru/C (5%wt), Ru/Al₂O₃ (5%wt), RuCl₃·xH₂O were purchased from Strem chemicals. 9,10-dihydroxy octadecanoic acid (75% GC purity), sunflower oil and rapeseed oil were supplied by Oleon. All new compounds were characterized by spectroscopic data. Reactions were monitored by TLC using aluminium silica gel (60F₂₅₄). They were carried out on a plate of 0.20 mm silica gel. For revelations, UV ($\lambda = 254$ nm) light was provided (Universal UV lamp CAMAC). A phosphomolybdic acid solution was used to reveal the TLC plate if necessary. Purification by flash chromatography was performed using silica gel 60H (40-63 μ m). Nuclear magnetic resonance spectra were recorded on a Brüker DRX 300 or Brüker ALS 300 (¹H-300 MHz, ¹³C-75 MHz). Chemical shifts are given in ppm with reference to residual DMSO or CHCl₃ central peaks: 2.50 and 7.26 ppm for proton, 39.52 and 77.16 ppm for carbon, respectively. *J* values are given in Hertz (Hz). Abbreviations are defined as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quadruplet, m = multiplet, br = broad. Mass spectra were performed in positive-ion mode on a hybrid quadrupole time-of-flight mass spectrometer (MicroTOFQ-II, Bruker Daltonics, Bremen) with an Electrospray Ionization (ESI) ion source. The flow of spray gas was at 0.6 bar and the capillary voltage was 4.5 kV. The solutions were injected at 180 μ L/h in a mixture of solvents (methanol/dichloromethane/water 45/40/15). The mass range of the analysis was 50-1000 m/z and the calibration was done with sodium formate. Infra-red (IR) spectra were recorded in a SMART iTR-Nicolet iS10 spectrometer using Attenuated Total Reflectance (ATR) and the wave numbers are expressed in cm⁻¹. Melting points were measured using a BUCHI Melting point (SMPIO) and noted in °C. A first estimate of the melting point of some of our solids was performed on a Köfler bench and SMP-10 Stuart machine.

2. GC method

Gas chromatography (GC) analyses for the 1,2-diols starting materials, the corresponding α -hydroxyketones and 1,2-diketone were performed using a Shimadzu GC (GC-2025) apparatus equipped with a ZB-5-MS capillary column (10 m, 0.10 mm i.d., 0.10 μ m film thickness). The carrier gas was N₂, at a flow rate of 0.43 mL/min and the injection mode is split (ratio 1:100). The column temperature was initially at 100°C for 1 min, and then was gradually increased to 260°C (25°C/min) and the temperature was kept at 260°C during 2.5 min. Finally, the temperature was increased to 315°C (45°C/min) and kept at 315°C during 2 min. The injector and FID temperature were respectively set at 300°C and 315°C.

3. General procedures

3.1 General procedures for the preparation of fatty α -hydroxyketones

a) Mono-oxidation of fatty 1,2-diols

In 30-mL steel reactor, methyl 9,10-dihydroxyoctadecanoate (4 g, 12 mmol), Pd(OAc)₂ (54 mg, 0.24 mmol, 2 mol% in Pd), neocuproine (50 mg, 0.24 mmol, 2 mol%) were successively introduced in MeOH (8 mL) under stirring. The mixture was stirring at room temperature in a few minutes until the medium became more homogeneous. Next, glacial acetic acid (43 mg, 0.72 mmol, 6 mol%) was added to the solution before closing the apparatus. Oxygen (3 bar) was charged in the reactor, then the reaction was heated at 50°C (oil bath) for 1.5 hour. The reaction mixture was cooled down to 25°C by stream of water before adding EtOAc (20 mL). The suspension was filtered and the filtrate was evaporated under reduced pressure to give a green oil (3.97 g). The crude product was purified by column chromatography on silica gel (CH₂Cl₂/EtOAc, 100:0 → 95:5) to give the α -hydroxyketone (3.20 g, 80%) as white solid. See Supporting Information for the full characterization of the compound.

b) Dehydrogenation of fatty 1,2-diols using Ru/C catalyst

In a Schlenk flash, methyl 9,10-dihydroxyoctadecanoate **1** (0.92 g, 2.8 mmol) and activated 5%-Ru/C (0.26 g, 5 mol% in Ru) were introduced. Then, argon was filled inside the equipment. The outline of apparatus was connected with evaporator system to control the vacuum pressure at 100 mbar. The reaction was heated at 175°C (oil bath) for 3 hours. After cooling to room temperature, EtOAc (2 x 20 mL) was added in the mixture then the resulting slurry was filtered through milipore system (pore 0.1 μ m). The filtrate was evaporated under reduced pressure to give the crude product (0.89 g). The residue was purified by column chromatography on silica gel (CH₂Cl₂/EtOAc, 100:0 → 95:5) to give α -hydroxyketone.

3.2 General procedures for the cleavage of fatty α -hydroxyketones

a) General procedure for cleavage of fatty α -hydroxyketones under microwave irradiation

In a 5-mL microwave tube, 9(10)-hydroxy-10(9)-oxooctadecanoate **12** (1:1 mixture of regioisomers) (65.7 mg, 0.2 mmol, 1 equiv), the thiazolium salt (0.04 mmol, 20 mol%) and K₂CO₃ (5.5 mg, 0.04 mmol, 20 mol%) were added. The tube was flushed with argon and dry CH₃CN (2 mL) was added. The mixture was stirred under microwave irradiation at the desired temperature for a period of time. The mixture was cooled down to room temperature and analyzed by GC using hexadecane as internal standard.

b) General procedure for cleavage of fatty α -hydroxyketones under reactive distillation conditions

In a 25-mL round bottom flask, under an argon atmosphere, K₂CO₃ (1.2 mmol, 165.8 mg, 10 mol%), 3-butyl-4,5-dimethylthiazol-3-ium triflate **85** (766.5 mg, 2.4 mmol, 20 mol%) and α -hydroxyketone (12 mmol) were added and the distillation set-up was

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installed (Figure 19). Then, the mixture was heated at 180°C (oil bath pre-heated at 180°C) under reduced pressure (vacuum = 1-3 mbar except in the case of α -hydroxyketone **28** and **86**). The distillate was collected, weighted and analysed by GC, using *n*-hexadecane as internal standard. The residue was also weighted and analyzed by GC and NMR. If needed, the aldehydes could be further purified by flash chromatography (Cyclohexane/EtOAc 100:0 \rightarrow 95:5). In some cases, the residue can be solubilized in EtOAc, then filtered through a Celite-545 and evaporated under reduced pressure to obtain a crude mixture. This mixture could be further purified by flash chromatography (Cyclohexane/EtOAc 100:0 \rightarrow 90:10) to give symmetrical α -hydroxyketones **89**, **90** and **91**.

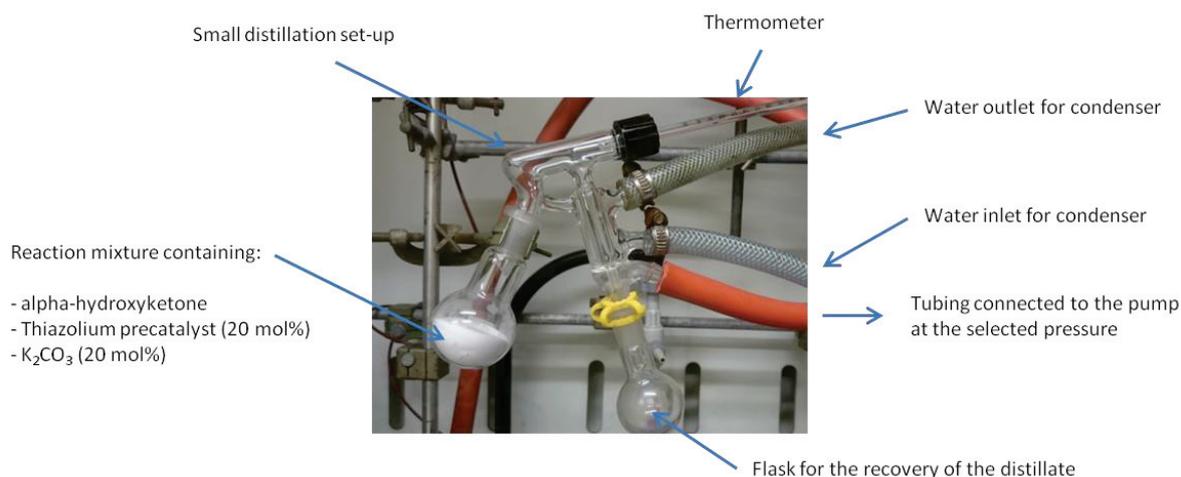


Figure 19: *The distillation setup (before distillation)*

3.3 General procedure for the Stetter reaction

In a 5-mL microwave tube, methyl azelaaldehyde (200 mg, 1.07 mmol, 1 equiv.), NHC precursor (0.21 mmol, 20 mol%), K₂CO₃ (15 mg, 10 mol%), Michael acceptor in desired quantity (5-10 equiv) were combined. Dry CH₃CN (1.5 or 2 mL) was added. The mixture was stirred under microwave irradiation at desired temperature, for a period of time. The mixture was cooled to room temperature and analyzed by GC (with or without hexadecane as an internal standard). Crude mixture reaction was filtered and the filtrate was concentrated under reduced pressure to give the residue. The residue was purified by flash column chromatography (Cyclohexane/EtOAc from 100:0 to 94:6) to give the Michael adducts.

3.4 General procedures for the cleavage of fatty 1,2-diketones

a) General procedure for the preparation of fatty 1,2-diketones

In a 250-mL 2-neck flask, fatty α -hydroxyketones (11 mmol) was suspended in MeCN (111 mL) and a solution of VOCl₃ (19 mg, 1 mol%) was added dropwise over a 15 minutes period in MeCN (0.11 mL). The flask was equipped with an oxygen balloon and the yellow suspension was stirred at room temperature for 24 hours. The reaction was quenched by a NaHCO₃ saturated solution (2x50 mL) and extracted with a mixture of heptane/EtOAc (1/1, 250 mL). The organic

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layer was washed with saturated NH_4Cl solution (2x75 mL), saturated NaCl solution (2x200 mL) and dried (MgSO_4), filtrated. The filtrate solution was evaporated under reduced pressure to give the crude mixture which was further purified by column chromatography to obtain fatty 1,2-diketones.

b) General procedure for the cleavage of fatty 1,2-diketones to corresponding esters

A fatty 1,2-diketone (3 mmol), NHC precursors (0.6 mmol, 20 mol%) and K_2CO_3 (414 mg, 3 mmol, 100 mol%) were introduced in a 25-mL round bottom flask under oxygen atmosphere (balloon), then MeOH (6 mL) was added. The mixture was heated at 65°C for 3 hours. After cooling to room temperature, MeOH was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) and the solution was filtrated through celite and the filtrate was evaporated under reduced pressure. The residue was dissolved in MeOH (2 mL) and a solution of sulfuric acid (1 wt%) was introduced until pH was around 5, then this mixture was esterified in the presence of Amberlyst-15 (20% w/w) for 18 hours. Finally, the mixture was filtered (to remove Amberlyst), evaporated under reduced pressure and further purified by flash chromatography (Cyclohexane/ EtOAc from 100:0 to 94:6) to give the corresponding esters in good yields.

3.5 General procedures for cleavage of fatty epoxide to aldehydes

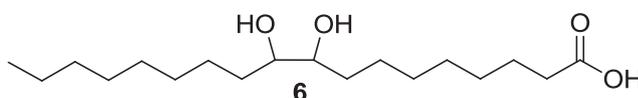
a) General procedure for the preparation of fatty β -hydroxy hydroperoxides

A fatty epoxide (6 mmol), phosphotungstic acid (0.06 mmol, 1 mol%), anhydrous MgSO_4 (18 mmol, 3 equiv) and t-amyl alcohol (12 mL, 0.5 M) were introduced in a 100-mL round bottom flask under argon atmosphere, a solution of hydrogen peroxide (50% H_2O_2 in H_2O , 1.1 equiv) was added dropwise in the mixture and the reaction was heated at 50°C for 1 hour. After the conversion was complete, the crude was filtrated through Celite-545 to remove the excess of MgSO_4 and phosphotungstic acid. This filtrate was evaporated under reduced pressure to give the crude mixture which was further purified by column chromatography (Cyclohexane/ EtOAc from 96:4 to 90:10) to provide the fatty β -hydroxy hydroperoxide as a colourless oil.

b) General procedure for the cleavage of β -hydroxy hydroperoxides to aldehydes

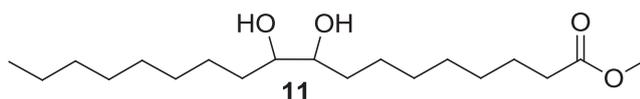
A fatty β -hydroxy hydroperoxide (1-3 mmol) and solvent (0.25M) were introduced in a 25-mL schlenk flask under atmospheric argon. Then, this mixture was heated at a suitable temperature (60 - 100°C) in a period of time (2-16 hours). When the reaction was completed, the mixture was cooled at room temperature and a mixture of products was analyzed by GC and $^1\text{H-NMR}$.

4. Characterisation of fatty 1,2-diols

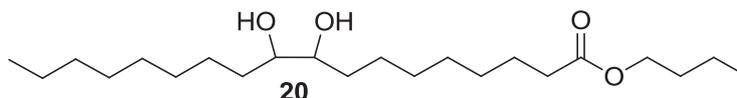


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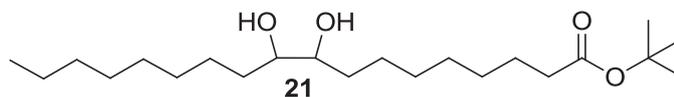
A white solid (mp = 105°C); **IR** (ν_{\max}): 3330 (O-H), 2951, 2913, 2847 (C-H stretching), 1701 (C=O), 1466, 1333, 1296, 891, 862, 791, 657, 549, 534; **HRMS-ESI**: calculated for $C_{18}H_{35}O_4$ $[M-H]^-$ 315.2527, found 315.2541; **1H -NMR** (300 MHz, d_6 -DMSO): δ_H = 0.85 (t, J = 6.7, 3H, CH_3), 1.24-1.49 (m, 26H, 13- CH_2), 2.17 (t, J = 7.3, 2H, CH_2CO), 3.17-3.21 (m, 2H, 2 $CH-OH$), 4.12-4.14 (m, 2H, O-H), 11.95-11.97 (br s, 1H, COOH); **^{13}C -NMR** (75 MHz, d_6 -DMSO): δ_C = 14.0 (CH_3), 22.2, 24.6, 25.71, 25.74, 28.7, 28.9, 29.0, 29.2, 29.3, 29.4, 31.4, 32.5, 32.5, 33.7 (14- CH_2), 73.2 (2xCH), 174.5 (C=O).



A white solid (mp = 90-92°C). **IR** (ν_{\max}): 3339, 3260 (O-H), 2951, 2928, 2913, 2846, 1740 (C=O), 1202, 1189, 1165, 1138, 1112 (C-O); **MS** (ESI^+) m/z = 313.3 ($[MH-H_2O]^+$, 45), 331.2 ($[MH]^+$, 100), 353.3 ($[MNa]^+$, 57); **HRMS-ESI**: calculated for $C_{19}H_{38}NaO_4$ $[MNa]^+$ 353.2662, found 353.2656; **1H -NMR** (300 MHz, $CDCl_3$): δ_H = 0.87 (t, J = 6.7, 3H, CH_3), 1.26-1.30 (m, 18H, 9- CH_2), 1.40-1.63 (m, 8H, 4- CH_2), 2.29 (t, J = 7.5, 2H, CH_2-CO), 3.38-3.40 (m, 2H, 2x $CH-OH$), 3.60 (s, 3H, CH_3O); **^{13}C -NMR** (75 MHz, $CDCl_3$): δ_C = 14.2 (CH_3), 22.8, 25.0, 25.7, 25.8, 29.1, 29.3, 29.4, 29.5, 29.7, 29.8, 32.0, 33.6, 33.7, 34.2 (14- CH_2), 51.6 (CH_3O), 74.57, 74.63 (2xCH), 174.5 (C=O).

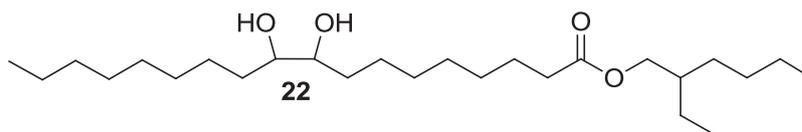


A white solid (mp = 53-55°C). **IR** (ν_{\max}): 3339 (br, O-H), 2912, 2847 (C-H stretching), 2530, 2159, 1977, 1736 (C=O ester), 1467, 1415, 1168, 1036, 764, 721, 648; **1H -NMR** (300 MHz, $CDCl_3$): δ_H = 0.87 (t, J = 6.8, 3H, CH_3), 0.93 (t, J = 7.3, 3H, CH_3), 1.26-1.36 (m, 20H, 10- CH_2), 1.37-1.60 (m, 10H, 5- CH_2), 1.95 (br s, 2H, 2-OH), 2.28 (t, J = 7.5, 2H, $CH_2-C=O$), 3.39-3.41 (m, 2H, 2- $CH-OH$), 4.06 (t, J = 6.7, 2H, CH_2O); **^{13}C -NMR** (75 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 14.2 (CH_3), 19.2, 22.8, 25.0, 25.7, 25.8, 29.2, 29.3, 29.4, 29.6, 29.7, 29.8, 30.8, 32.0, 33.6, 33.7, 34.5 (16- CH_2), 64.3 (CH_2), 74.5, 74.6 (2xCH), 174.2 (C=O); **HRMS-ESI**: calculated for $[M+H]^+$, $C_{22}H_{45}O_4$: 373.3300, found 373.3312.

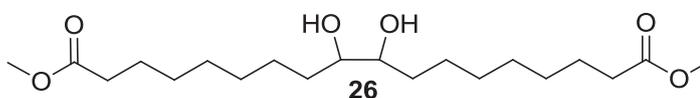


A white solid (mp=63-65°C). **IR** (ν_{\max}): 3340 (br, O-H), 2914, 2847 (C-H stretching), 2512, 2160, 1732 (C=O), 1466, 1154, 720, 649; **1H -NMR** (300 MHz, $CDCl_3$): δ_H = 0.88 (t, J = 6.7, 3H, CH_3), 1.27-1.37 (m, 20H, 10- CH_2), 1.44 (s, 9H, 3- CH_3), 1.47-1.59 (m, 6H, 3- CH_2), 1.94 (br s, 2H, 2-OH), 2.20 (t, J = 7.5, 2H, $CH_2-C=O$), 3.39-3.41 (m, 2H, 2- $CH-OH$); **^{13}C -NMR** (75 MHz, $CDCl_3$): δ_C = 14.2 (CH_3), 22.8, 25.1, 25.7, 25.8 (4- CH_2), 28.2 (3x CH_3), 29.1, 29.3, 29.4, 29.6, 29.7, 29.8, 32.0, 33.6, 33.7, 35.7 (10- CH_2), 74.7 (2x $CH-OH$), 80.2 (C_q), 173.6 (C=O); **HRMS-ESI**: calculated for $[M+H]^+$, $C_{22}H_{45}O_4$: 373.3300, found 373.3301.

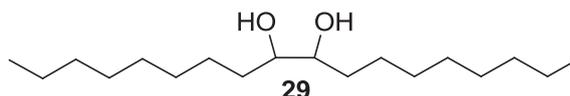
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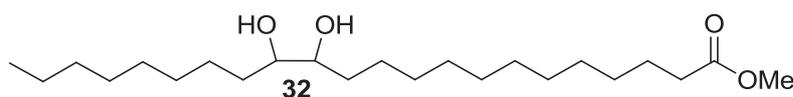
A white solid (mp = 41-43°C). **IR** (ν_{\max}): 3341 (br, O-H), 2913, 2847 (C-H stretching), 2159, 2026, 1737, 1466, 1202, 1167, 722, 650; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 0.85-0.91 (m, 9H, 3- CH_3), 1.27-1.39 (m, 26H, 13- CH_2), 1.40-1.64 (m, 9H, 4- CH_2 +1- CH), 1.93 (br s, 2H, 2-OH), 2.29 (t, J = 7.5, 2H, CH_2 -C=O), 3.38-3.41 (m, 2H, 2x CH-OH), 3.98 (dd, J = 5.8, 0.7, 2H, OCH_2); **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): δ_{C} = 11.1 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 22.8, 23.1, 23.9, 25.1, 25.7, 25.8, 29.0, 29.2, 29.3, 29.4, 29.6, 29.7, 29.8, 30.5, 32.0, 33.65, 33.69, 34.5, 38.8 (19- CH_2), 66.8 (CH_2), 74.54, 74.59 (2x CH-OH), 174.3 (C=O); **HRMS-ESI**: calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{26}\text{H}_{53}\text{O}_4$: 429.3922, found 429.3938.



A white solid (mp = 81-83°C). **IR** (ν_{\max}): 3333 (br, O-H), 2912, 2847 (C-H stretching), 2362, 2160, 1976, 1742 (C=O ester), 1319, 1225, 1167, 1078, 882, 870, 750, 719, 653 cm^{-1} ; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 1.25-1.52 (m, 20H, 10- CH_2), 1.59-1.64 (m, 4H, 2- CH_2), 1.99 (br s, 2H, 2xO-H), 2.30 (t, J = 7.5, 4H, 2x CH_2 -C=O), 3.35-3.45 (m, 2H, 2x CH-OH), 3.66 (s, 6H, 2 x CH_3O); **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): δ_{C} = 24.9 (2x CH_2), 25.6 (2x CH_2), 29.1 (2x CH_2), 29.2 (2x CH_2), 29.5 (2x CH_2), 33.6 (2x CH_2), 34.1 (2x CH_2), 51.5 (2x CH_3O), 74.5 (2x CH-OH), 174.5 (2x C=O); **HRMS-ESI**: calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{20}\text{H}_{31}\text{O}_6$: 375.2732, found 375.2741.



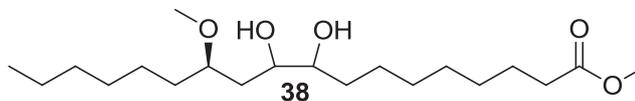
A white solid (mp = 109-111°C). **IR** (ν_{\max}): 3255 (br, O-H), 2954, 2916, 2848, 2520, 2361, 2160, 1976, 1466, 1122, 1048, 908, 871, 720, 668 cm^{-1} ; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 0.88 (t, J = 6.7, 6H, 2x CH_3), 1.27-1.47 (m, 28H, 14- CH_2), 1.75-2.11 (br s, 2H, 2-OH), 3.37-3.43 (m, 1H, CH(OH)), 3.58-3.61 (m, 1H, CH(OH)); **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): δ_{C} = 14.2 (2x CH_3), 22.8 (2x CH_2), 25.8, 26.2 (2- CH_2), 29.4 (2x CH_2), 29.7 (2x CH_2), 29.8 (2x CH_2), 32.0 (2x CH_2), 31.3, 33.8 (2- CH_2), 74.7, 74.9 (2- CH); **HRMS-ESI**: calculated for $[\text{M}+\text{Na}]^+$, $\text{C}_{18}\text{H}_{38}\text{NaO}_2$: 309.2753, found 309.2764.



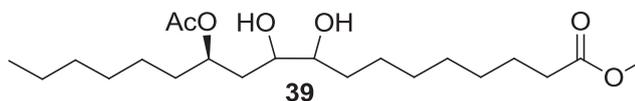
A white solid (mp = 78-80°C). **IR** (ν_{\max}): 3330 (br, O-H), 2912, 2847 (C-H stretching), 2159, 1742 (C=O ester), 1467, 1142, 904, 750, 720, 653; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 0.88 (t, J = 6.6, 3H, CH_3), 1.26-1.64 (m, 34H, 17- CH_2), 2.03 (br s, 2H, O-H), 2.31 (t, J = 7.5, 2H, CH_2 -C=O), 3.40-

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3.42 (m, 2H, 2xCH-OH), 3.66 (s, 3H, CH₃O); ¹³C-NMR (75 MHz, CDCl₃): δ_c = 14.2 (CH₃), 22.8, 25.0 (2-CH₂), 25.8 (2xCH₂) 29.2, 29.3, 29.4, 29.5, 29.64 (5-CH₂), 29.67 (3xCH₂), 29.78, 29.80, 31.97 (3-CH₂), 33.7 (2xCH₂), 34.2 (CH₂), 51.6 (CH₃O), 74.6 (2xCH-OH), 174.6 (C=O); **HRMS-ESI**: calculated for [M+H]⁺, C₂₃H₄₇O₂: 387.3474, found 387.3464.

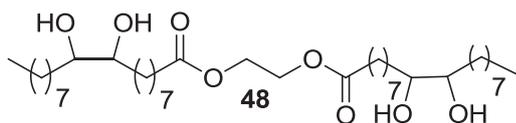


A colourless oil (a mixture of two inseparable isomers dr= 40:60); ¹H NMR (300 MHz, CDCl₃): δ_H = 0.86 (t, J= 6.7, 3H, CH₃), 1.20-1.85 (m, 24H, 12-CH₂), 2.28 (t, J=7.5, 2H, CH₂C=O), 2.88 (br s, 2H, O-H), 3.26-3.39 (m, 1H, CH-OMe), 3.339 (s, 3H, OCH₃ in major isomer), 3.341 (s, 3H, OCH₃ in minor isomer), 3.64 (s, 3H, COOCH₃), 3.40-3.50 and 3.55-3.71 (m, 2H, CH-OH); ¹³C NMR (75 MHz, CDCl₃): δ_c = 14.2 (2xCH₃), 22.7 (2xCH₂), 25.00 (2xCH₂), 24.5 (CH₂ in minor isomer), 25.4 (CH₂ in major isomer), 25.7 (CH₂ in minor isomer), 25.8 (CH₂ in major isomer), 29.2 (2xCH₂ in minor isomer), 29.3 (2xCH₂ in major isomer), 29.53 (CH₂ in major isomer), 29.60 (CH₂ in minor isomer), 29.56 (2xCH₂), 31.9 (2xCH₂), 32.9 (CH₂ in minor isomer), 33.0 (CH₂ in major isomer), 33.5 (CH₂ in major isomer), 33.7 (CH₂ in minor isomer), 34.2 (2xCH₂), 36.2 (CH₂ in major isomer), 37.2 (CH₂ in minor isomer), 51.5 (2xCH₃O), 56.0 (CH₃O in minor isomer), 56.8 (CH₃O in major isomer), 71.6 (CH in major isomer), 74.2 (CH in minor isomer), 74.6 (CH in major isomer), 74.7 (CH in minor isomer), 79.3 (CH₃ in major isomer), 81.9 (CH₃ in minor isomer), 174.4 (2xC=O); **HRMS-ESI**: calculated for [M+Na]⁺, C₂₀H₄₀NaO₅: 383.2772, found 383.2768

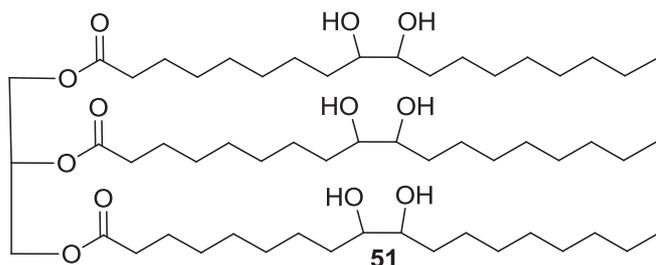


A colourless oil. **IR** (ν_{max}): 3440 (br, O-H), 2926, 2855, 2159, 1734 (C=O), 1436, 1371, 1239, 1022, 847, 704; ¹H-NMR (300 MHz, CDCl₃): δ_H = 0.83 (t, J = 6.6, 3H, CH₃), 1.23-1.74 (m, 24H, 12-CH₂), 1.99 and 2.04 and 2.05 and 2.07 (4s, 3H, CH₃-C=O in 4 isomers), 2.26 (t, J = 7.5, 2H, CH₂-C=O), 2.92 (br s, 2H, 2xO-H), 3.24-3.46 and 3.77-3.88 (m, 2H, 2xCH-OH), 4.75-4.82 and 4.92-5.03 (m, 1H, CH-OAc); ¹³C-NMR (75 MHz, CDCl₃): δ_c = 14.1 (CH₃), 21.07, 21.15, 21.19, 21.4 (4xCH₃-C=O in 4 isomers), 22.60, 22.64, 24.9, 25.2, 25.3, 25.4, 25.6, 25.7, 25.75, 25.82, 29.1, 29.17, 29.2, 29.3, 29.5, 30.1, 31.7, 31.8, 33.3, 33.5, 34.1, 34.3, 35.0, 37.5, 38.2, 38.4, 38.9 (multi-signal CH₂), 51.5 (CH₃O), 67.7, 70.4, 71.9, 72.0, 72.9, 73.2, 74.2, 74.4 (multi-signal CH-OH), 171.0, 171.1, 171.2, 171.3 (4-C=O in 4 isomers), 174.39, 174.42 (C=O ester); **HRMS-ESI**: calculated for [M+Na]⁺, C₂₁H₄₀NaO₆: 411.2723, found 411.2698

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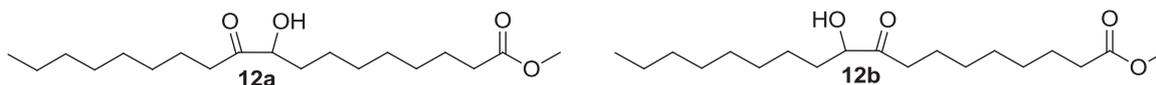
A white solid, $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): $\delta_{\text{H}} = 0.85$ (t, $J = 6.6$, 3H, CH_3), 1.24-1.52 (m, 52H, 26- CH_2), 2.28 (t, $J = 7.5$, 4H, $2\times\text{CH}_2\text{-C=O}$), 3.19 (m, 4H, $4\times\text{CH}$), 4.13 (d, $J = 5.3$, 4H, $4\times\text{O-H}$), 4.20 (s, 4H, $2\times\text{OCH}_2$); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 13.9$ ($2\times\text{CH}_3$), 22.2 ($2\times\text{CH}_2$), 24.5 ($2\times\text{CH}_2$), 25.6 ($2\times\text{CH}_2$), 25.7 ($2\times\text{CH}_2$), 28.5 ($2\times\text{CH}_2$), 28.8 ($2\times\text{CH}_2$), 28.9 ($2\times\text{CH}_2$), 29.1 ($2\times\text{CH}_2$), 29.2 ($2\times\text{CH}_2$), 29.4 ($2\times\text{CH}_2$), 31.4 ($2\times\text{CH}_2$), 32.4 ($2\times\text{CH}_2$), 33.5 ($2\times\text{CH}_2$), 61.8 ($2\times\text{CH}_2\text{O}$), 73.2 ($4\times\text{CH}$), 172.7 ($2\times\text{C=O}$); **HRMS-ESI**: calculated for $[\text{M}+\text{Na}]^+$, $\text{C}_{38}\text{H}_{74}\text{NaO}_8$: 681.5276, found 681.5248



A sticky solid containing 71% Tris(diols-oleic), 5% Tris(tetraol-linoleic) and 8% monoketone oleic (confirmed by $^1\text{H-NMR}$ and GC). **IR** (ν_{max}): 3359 (br, O-H), 2918, 2850 (C-H stretching), 2361, 2311, 1740 (C=O), 1462, 1415, 1377, 1072, 841, 721, 668; $^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.86$ (t, $J = 6.6$, 9H, 3- CH_3), 1.25-1.40 (m, 60H, 30- CH_2), 1.40-1.63 (m, 18H, 9- CH_2), 2.31 (t, $J = 7.5$, 6H, $3\times\text{CH}_2\text{-C=O}$), 2.54-2.76 (br s, 6H, CH-OH oleic, 70%), 3.20-3.36 (m, 6H, CH-OH oleic, 70%), 4.09-4.16 and 4.26-4.31 (2m, 4H, $2\times\text{OCH}_2\text{-glycerol}$), 5.20-5.29 (m, 1H, OCH-glycerol); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 14.2$ (3- CH_3), 22.6, 24.8, 25.6, 25.7, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.8, 33.5, 33.6, 33.9, 34.1 (42-CH_2), 62.1 (2-OCH_2 glycerol), 69.0 (1-OCH glycerol), 74.6 (6- CH(OH)) 172.8, 173.2, 173.3 (3- C=O).

Visible peaks for linoleic: 3.45-3.58 (m, 12H, CH-OH linoleic, about 5-6%). Visible peaks for monoketone: 2.35 (t, $J = 7.3$, 12H, CH_2 in monoketone, about 8%).

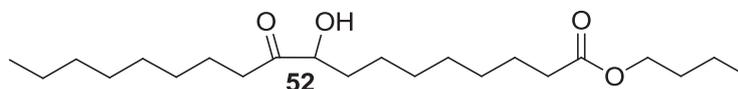
5. Characterisation of fatty α -hydroxyketones



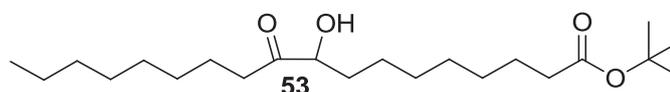
A white solid (mp = 36-40°C). **IR** (ν_{max}): 3317 (br, O-H), 2931, 2915, 2849, 1735 (C=O ester), 1710 (C=O ketone), 1245, 1215, 1177, 1105, 1087 (C-O); $^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.82$ (t, $J = 6.6$, 3H, CH_3), 1.14-1.33 (m, 17H), 1.35-1.64 (m, 6H, 3- CH_2), 1.64-1.85 (m, 1H), 2.24 (t, $J = 7.5$, 2H, $\text{CH}_2\text{-C=O}$ ester), 2.40 (dd, $J = 12.5$, 7.2, 2H, $\text{CH}_2\text{-C=O}$ ketone), 3.52 (br s, 1H, O-H), 3.63 (s, 3H, CH_3O), 4.08-4.12 (m, 1H, CH-OH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 14.1$ (CH_3), 22.6 (CH_2), 23.5 and 23.6 (CH_2), 24.8 and 24.9 (CH_2), 28.9 and 29.00 (CH_2), 29.02 (CH_2), 29.08 and

EXPERIMENTAL SECTION

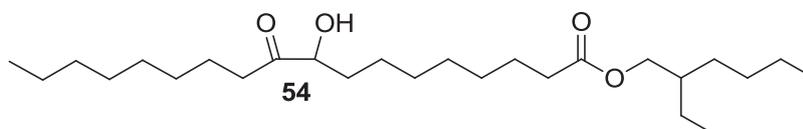
29.12 (CH₂), 29.24, 29.25, 29.33 (3-CH₂), 29.44 and 29.48 (CH₂), 31.81 and 31.86 (CH₂), 33.73 and 33.79 (CH₂), 34.00 and 34.04 (CH₂), 37.78 and 37.85 (CH₂), 51.4 (CH₃O), 76.38 and 76.44 (CH-OH), 174.19 and 179.24 (C=O ester), 212.51 and 212.56 (C=O ketone); **ESI-MS**: $m/z = 329.3$ ([M+H]⁺, 100), 351.2 ([M+Na]⁺, 55), 678.8 ([2M+Na]⁺, 58); **HRMS-ESI**: calculated for [M+Na]⁺, C₁₉H₃₆NaO₄: 351.2506, found 351.2502.



A white solid (mp= 35-38°C). **IR** (ν_{\max}): 3322 (br, O-H), 2955, 2914, 2849 (C-H stretching), 2159, 2029, 1731 (C=O ester), 1710 (C=O ketone), 1462, 1183, 1087, 924, 751, 699, 660; **¹H-NMR** (300 MHz, CDCl₃): $\delta_{\text{H}} = 0.87$ (t, $J = 6.7$, 3H, CH₃), 0.94 (t, $J = 7.3$, 3H, CH₃), 1.27-1.50 (m, 22H, 11-CH₂), 1.50-1.83 (m, 8H, 4-CH₂), 2.28 (t, $J = 7.5$, 2H, CH₂-C=O ester), 2.38-2.51 (m, 2H, CH₂-C=O ketone), 3.48 (br s, 1H, O-H), 4.06 (t, $J = 6.7$, 2H, CH₂O), 4.13-4.17 (m, 1H, CH-OH); **¹³C-NMR** (75 MHz, CDCl₃): $\delta_{\text{C}} = 13.8$ (CH₃), 14.2 (CH₃), 19.23 (CH₂), 22.71 and 22.73 (CH₂), 23.6 and 23.7 (CH₂), 24.88 and 24.92 (CH₂), 24.97 and 25.01 (CH₂), 28.99 and 29.07 (CH₂), 29.10 (CH₂), 29.18 (CH₂), 29.29 and 29.31 (CH₂), 29.34 and 29.39 (CH₂), 29.50 and 29.54 (CH₂), 30.78 (CH₂), 31.87 and 31.92 (CH₂), 33.80 and 33.86 (CH₂), 34.37 and 37.40 (CH₂), 37.85 and 37.92 (CH₂), 64.19 and 64.21 (CH₂O), 76.43 and 76.49 (CH-OH), 173.95 and 174.00 (C=O ester), 212.55 and 212.61 (C=O ketone); **HRMS-ESI**: calculated for [M+Na]⁺, C₂₂H₄₂NaO₄: 393.2975, found 393.2966.

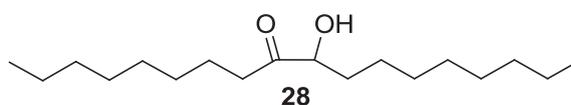


A white solid (mp= 35-38°C). **IR** (ν_{\max}): 3333 (br, O-H), 2914, 2848 (C-H stretching), 1732 (C=O ester), 1711 (C=O ketone), 1417, 1104, 752, 726, 701, 658; **¹H-NMR** (300 MHz, CDCl₃): $\delta_{\text{H}} = 0.87$ (t, $J = 6.7$, 3H, CH₃), 1.20-1.38 (m, 18H, 9-CH₂), 1.43 (s, 9H, 3xCH₃), 1.50-1.85 (m, 6H, 3-CH₂), 2.19 (t, $J = 7.5$, 2H, CH₂-C=O ester), 2.37-2.50 (m, 2H, CH₂-C=O), 3.43 (br s, 1H, O-H), 4.13-4.18 (m, 1H, CH-OH); **¹³C-NMR** (75 MHz, CDCl₃): $\delta_{\text{C}} = 14.2$ (CH₃), 22.71 and 22.72 (CH₂), 23.6 and 23.7 (CH₂), 24.88 and 24.92 (CH₂), 25.06 and 25.09 (CH₂), 28.2 (3xCH₃), 28.93 and 29.05 (CH₂), 29.10 and 29.12 (CH₂), 29.18 and 29.20 (CH₂), 29.29 and 29.31 (CH₂), 29.35 and 29.39 (CH₂), 29.50 and 29.54 (CH₂), 31.87 and 31.91 (CH₂), 33.80 and 33.85 (CH₂), 35.58 and 35.62 (CH₂), 37.86 and 37.92 (CH₂), 76.43 and 76.49 (CH-OH), 79.98 and 80.02 (C(CH₃)₃), 173.29 and 173.34 (C=O ester), 212.58 and 212.63 (C=O ketone); **HRMS-ESI**: calculated for [M+Na]⁺, C₂₂H₄₂NaO₄: 393.2975, found 393.2966.

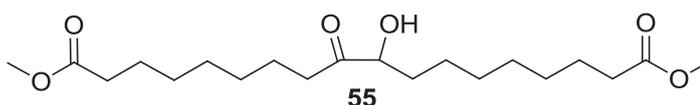


EXPERIMENTAL SECTION

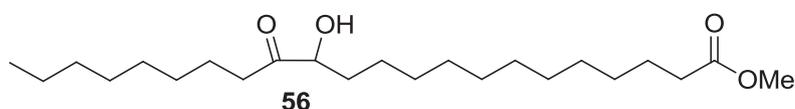
A colourless liquid. **IR** (ν_{\max}): 2924, 2855 (C-H stretching), 2159, 2029, 1976, 1734 (C=O ester), 1710 (C=O ketone), 1462, 1171, 724, 647; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 0.73-0.82 (m, 9H, 3- CH_3), 1.13-1.29 (m, 26H, 13- CH_2), 1.32-1.74 (m, 8H, 4- CH_2), 2.19 (t, J = 7.5, 2H, $\text{CH}_2\text{-C=O}$ ester), 2.27-2.42 (m, 2H, $\text{CH}_2\text{-C=O}$ ketone), 3.38 (br s, 1H, O-H), 3.87 (dd, J = 5.8, 0.8, 2H, CH_2O), 4.02-4.08 (m, 1H, CH-OH); **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): δ_{C} = 11.1, 14.11, 14.15 (3- CH_3), 22.71 and 22.72 (CH_2), 23.1 (CH_2), 23.6 and 23.7 (CH_2), 23.9 (CH_2), 24.88 and 24.91 (CH_2), 24.99 and 25.03 (CH_2), 28.99 (2x CH_2), 29.08 and 29.11 (CH_2), 29.18 (CH_2), 29.29 and 29.31 (CH_2), 29.35 and 29.38 (CH_2), 29.50 and 29.54 (CH_2), 30.5 (CH_2), 31.87 and 31.91 (CH_2), 33.80 and 33.85 (CH_2), 34.40 and 34.45 (CH_2), 37.84 and 37.91 (CH_2), 38.8 (CH_2), 66.7 (CH_2O), 76.4 and 76.5 (CH-OH), 173.9 (C=O ester), 212.4 (C=O ketone); **HRMS-ESI**: calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{26}\text{H}_{51}\text{O}_4$: 427.3775, found 427.3782.



A white solid (mp= 46-48°C). **IR** (ν_{\max}): 3319-3231 (br, O-H), 2953, 2915, 2872, 2848, 1710 (C=O), 1462, 1405, 1374, 1335, 1254, 1127, 1091 (C-O), 1031, 908, 831, 701; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 0.88 (t, J = 6.7, 6H, 2- CH_3), 1.20-1.37 (m, 20H, 10- CH_2), 1.42-1.80 (m, 6H, 3- CH_2), 2.36-2.51 (m, 2H, $\text{CH}_2\text{-C=O}$), 3.48 (d, J = 4.9, 1H, O-H), 4.16-4.19 (m, 1H, CH-OH); **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): δ_{C} = 14.16 (CH_3) 14.17 (CH_3), 22.73, 22.75, 23.7, 24.9, 29.2, 29.32, 29.33, 29.4, 29.5, 29.6 31.89, 31.94, 33.9, 37.9 (14- CH_2), 76.5 (CH), 212.6 (C=O); **MS (ESI $^+$)** m/z = 307.3 ($[\text{M}+\text{Na}]^+$, 100); **HRMS-ESI**: calculated for $[\text{M}+\text{Na}]^+$, $\text{C}_{18}\text{H}_{36}\text{NaO}_2$: 307.2608, found 307.2605 (0.9 ppm).

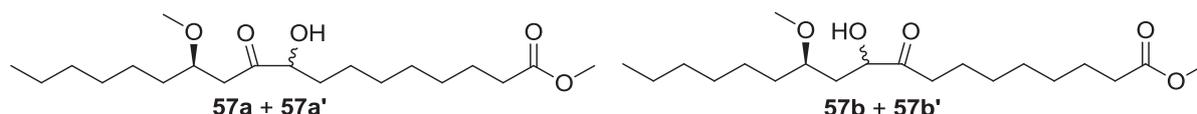


A white solid (mp = 43-46°C). **IR** (ν_{\max}): 3490-3349 (br, O-H), 2916, 2846, 1737 (C=O), 1708 (C=O), 1463, 1435, 1383, 1367, 1301, 1262, 1212, 1171, 1099, 1081, 1041, 977, 927, 882, 761, 721, 682; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 1.20-1.43 (m, 14H), 1.43-1.81 (m, 8H, 4- CH_2), 2.24 (t, J = 7.5, 4H, 2x $\text{CH}_2\text{-C=O}$ ester), 2.36-2.48 (m, 2H, $\text{CH}_2\text{-C=O}$ ketone), 3.35 (br s, 1H, O-H), 3.60 (s, 6H, 2x CH_3O), 4.07-4.10 (m, 1H, CH-OH); **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): δ_{C} = 23.5, 24.81, 24.83, 24.87, 28.89, 28.98 (6- CH_2), 29.0 (2x CH_2), 29.1, 29.2, 33.7, 34.00, 34.03, 37.77 (6- CH_2), 51.4 (2x CH_3O), 76.4 (CH-OH), 174.20, 174.24 (2-C=O ester), 212.5 (C=O ketone); **MS (ESI $^+$)**: m/z = 373.3 ($[\text{M}+\text{H}]^+$, 100), 395.3 ($[\text{M}+\text{Na}]^+$, 71); **HRMS-ESI**: calculated for $[\text{M}+\text{Na}]^+$, $\text{C}_{20}\text{H}_{36}\text{NaO}_6$: 395.2404, found 395.2394 (2.5 ppm).

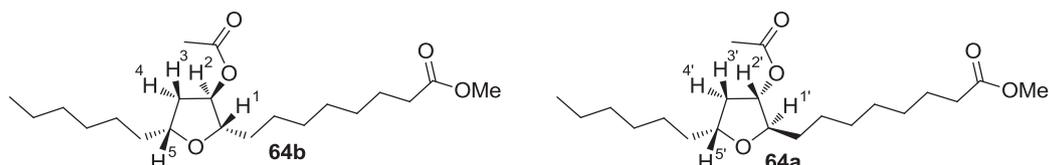


EXPERIMENTAL SECTION

A white solid (mp= 50-52°C); **IR** (ν_{\max}): 2914, 2848 (C-H stretching), 2160, 1977, 1735 (C=O ester), 1710 (C=O ketone), 1228, 1091, 1027, 995, 885, 773, 661, 571; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 0.83 (t, J = 6.7, 3H, CH_3), 1.18-1.31 (m, 26H, 13- CH_2), 1.35-1.80 (m, 6H, 3- CH_2), 2.24 (t, J = 7.5, 2H, $\text{CH}_2\text{-C=O}$ ester), 2.32-2.49 (m, 2H, $\text{CH}_2\text{-C=O}$ ketone), 3.36 (br s, 1H, O-H), 3.61 (s, 3H, CH_3O), 4.10-4.14 (m, 1H, CH-OH); **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): δ_{C} = 14.1 (CH_3), 22.7, 23.7, 24.9, 24.98, 29.14, 29.17 (6- CH_2), 29.3 (2x CH_2), 29.35, 29.42, 29.45, 29.46, 29.50, 29.54 (6- CH_2), 31.83 and 31.88 (CH_2), 33.8, 34.1, 37.9 (3- CH_2), 51.4 (CH_3O), 76.4 (CH-OH), 174.3 (C=O ester), 212.6 (C=O ketone); **HRMS-ESI**: calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{23}\text{H}_{45}\text{O}_4$: 385.3301, found 385.3312.



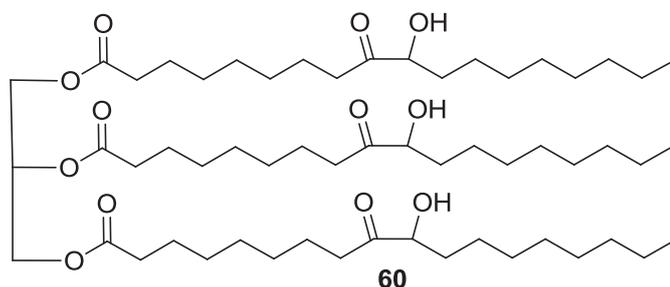
A colourless oil (a mixture of four inseparable isomers dr= 25:18:21:36, based on ratio of ^{13}C -NMR in α -hydroxyketones); **$^1\text{H NMR}$** (300 MHz, CDCl_3): δ_{H} = 0.87 (t, J = 6.7, 3H, CH_3), 1.15-2.10 (m, 22H, 11- CH_2), 2.29 (t, J =7.5, 2H, $\text{CH}_2\text{C=O}$), 2.35-2.85 (m, 2H, $\text{CH}_2\text{-C=O}$), 3.10 (s, 3H, CH_3O in isomer 1), 3.28 (s, 3H, CH_3O in isomer 2), 3.31 (s, 3H, CH_3O in isomer 3), 3.39 (s, 3H, CH_3O in isomer 4), 3.25-3.35, 3.37-3.43, 3.44-3.52 and 3.63-3.72 (m, 1H, CH-OMe in 4 isomers), 3.65 (s, 3H, CH_3O), 4.08-4.18 (m, CH-OH in isomer 1,2 and 3), 4.33 (dd, J = 10.1, 2.4, 1H, CH-OH in isomer 4); **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): δ_{C} = 14.1 (4x CH_3 in 4 isomers), 22.6 (4x CH_2 in 4 isomers), 23.5, 23.6, 24.78, 24.82 (4C, CH_2 in each isomer), 24.84, 24.86, 24.91, 24.96 (8C, 2- CH_2 in each isomer), 28.89, 28.92, 29.20, 29.21 (4C, CH_2 in each isomer), 28.97, 28.99, 29.01, 29.07 (8C, 2- CH_2 in each isomer), 29.31, 29.33, 29.46, 29.51 (4C, CH_2 in each isomer), 31.8 (4C, CH_2 in each isomer), 33.17, 33.20, 33.32, 33.50 (4C, CH_2 in each isomer), 33.69, 33.91, 33.97, 33.99 (4C, CH_2 in each isomer), 38.6 (4C, CH_2 in each isomer), 37.6 ($\text{CH}_2\text{C=O}$ in isomer 1), 37.9 ($\text{CH}_2\text{C=O}$ in isomer 4), 42.7 ($\text{CH}_2\text{C=O}$ in isomer 3), 42.8 ($\text{CH}_2\text{C=O}$ in isomer 2), 51.4 (4C, CH_3O in each isomer), 56.5 (CH_3O in isomer 1), 57.1 (CH_3O in isomer 3), 57.21 (CH_3O in isomer 2), 57.24 (CH_3O in isomer 4), 74.11, 74.14, 76.54, 76.98 (4C, CH-OH in each isomer), 77.3, 77.5, 77.7, 77.8 (4C, CH-OMe in each isomer), 174.13, 174.16 (4C, $\text{C=O}_{\text{ester}}$ in each isomer), 211.6, 211.7, 213.2, 213.2 (4C, $\text{C=O}_{\text{ketone}}$ in each isomer); **HRMS-ESI**: calculated for $[\text{M}+\text{Na}]^+$, $\text{C}_{20}\text{H}_{38}\text{NaO}_5$: 381.2607, found 381.2611.



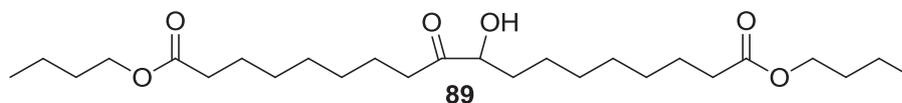
A colourless liquid. **IR** (ν_{\max}): 2922, 2855 (C-H stretching), 1737 (C=O), 1435, 1365, 1238, 1197, 1171, 1104, 1022, 705; **$^1\text{H-NMR}$** (300 MHz, CDCl_3): δ_{H} = 0.84 (t, J = 6.6, 3H, CH_3), 1.24-1.62 (m, 23H, 11- CH_2 + H^{A}), 1.68 (ddd, J = 10.9, 8.9, 5.1, 1H, H^{A}), 1.90 (ddd, J = 13.6, 5.2, 1.5, 1H, H^{B}), 2.011, 2.013 (s, 3H, $\text{CH}_3\text{-C=O}$), 2.26 (t, J = 7.5, 2H, $\text{CH}_2\text{-C=O}$), 2.33-2.44 (m, 1H, H^{C}),

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3.62 (s, 3H, CH₃O), 3.75 (td, $J = 6.4, 2.8$, 1H, H⁵), 3.86-3.99 (m, 2H, H^{1,1'} and H^{5'}), 4.84-4.90 (m, 1H, H^{2,2'}); ¹³C-NMR (75 MHz, CDCl₃): δ_c for the major isomer = 14.2 (CH₃), 21.3 (CH₃), 22.7 (CH₂), 24.98 (CH₂), 25.6 (CH₂), 26.08 (CH₂), 29.1 (CH₂), 29.2 (CH₂), 29.37 (CH₂), 29.45 (CH₂), 31.85 (CH₂), 34.4 (CH₂), 34.1 (CH₂), 35.6 (CH₂), 38.4 (CH₂), 51.5 (OCH₃), 78.5 (CH), 79.0 (CH), 83.9 (CH), 170.8 (C=O), 174.4 (C=O), δ_c for the minor isomer = 14.2 (CH₃), 21.3 (CH₃), 22.7 (CH₂), 24.98 (CH₂), 26.7 (CH₂), 26.14 (CH₂), 29.1 (CH₂), 29.2 (CH₂), 29.38 (CH₂), 29.45 (CH₂), 31.88 (CH₂), 32.7 (CH₂), 34.1 (CH₂), 36.1 (CH₂), 37.6 (CH₂), 51.5 (OCH₃), 77.4 (CH), 78.8 (CH), 82.7 (CH), 170.9 (C=O), 174.4 (C=O) (COSY, HSQC, HMBC were also used for determination the structure of compounds); **MS (ESI⁺)**: 311.3 [M-OAc]⁺, 371.3 [M+H]⁺, 393.3 [M+Na]⁺, 763.5 [2M+Na]⁺; **HRMS-ESI**: calculated for [M+Na]⁺, C₂₁H₃₈NaO₅: 393.2611, found 393.2611.

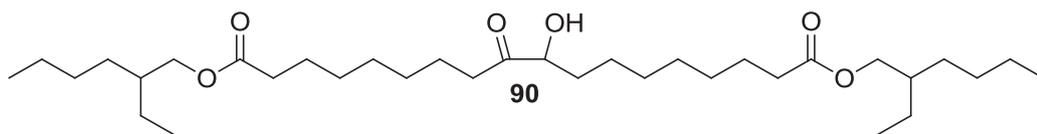


A viscous liquid. **IR** (ν_{\max}): 3460 (br, O-H), 2919, 2851 (C-H stretching), 1740 (C=O), 1465, 1372, 1238, 1164, 1046, 722, 634, 607; ¹H-NMR (300 MHz, CDCl₃): $\delta_H = 0.87$ (t, $J = 6.7$, 9H, 3-CH₃), 1.25-1.33 (m, 60H, 30-CH₂), 1.42-1.88 (m, 18H, 9-CH₂), 2.31 (t, $J = 7.5$, 6H, 3xCH₂-C=O), 2.35-2.53 (m, 6H, 3xCH₂-C=O), 3.23-3.42 (m, 6H, CH-OH in tris(diol)), 3.56 (br, O-H), 4.08-4.19 (m, 3H, 3xCH-OH in hydroxyketone, about 40%), 4.14 (dd, $J = 11.8, 6.0$, 2H, OCH₂-glycerol), 4.29 (dd, $J = 11.8, 4.0$, 2H, OCH₂-glycerol), 5.26-5.28 (m, 1H, OCH-glycerol); ¹³C-NMR (75 MHz, CDCl₃): $\delta_c = 14.1$ (CH₃), 22.6-42.7 (multi-signals CH₂), 62.0 (CH₂O), 68.8 (CH), 74.3, 74.4 (CH-OH in diol), 76.3, 76.4 (CH-OH in hydroxyketone), 172.7, 173.1 (C=O ester), 212.5 (C=O ketone).

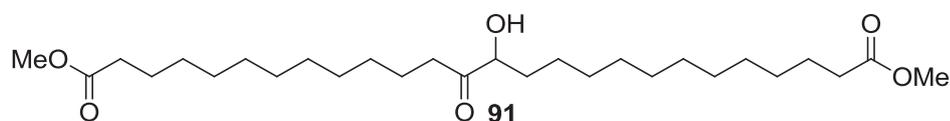


A green oil; ¹H NMR (300 MHz, CDCl₃): $\delta_H = 0.92$ (t, $J = 6.7$, 6H, 2xCH₃), 1.22-1.87 (m, 30H, 15-CH₂), 2.27 (t, $J = 7.5$, 4H, 2xCH₂-C=O), 2.35-2.50 (m, 2H, CH₂-C=O), 3.29 (br s, O-H), 4.05 (t, $J = 6.7$, 4H, 2xOCH₂), 4.14 (dd, $J = 7.2, 3.7$, CH-OH); ¹³C NMR (75 MHz, CDCl₃): $\delta_c = 13.7$ (2xCH₃), 19.2 (2xCH₂), 23.5, 24.82, 24.89, 24.93, 28.91, 29.00 (6-CH₂), 29.03 (2xCH₂), 29.1, 29.3 (2-CH₂), 30.7 (2xCH₂), 33.7, 34.29, 34.32 (3-CH₂), 37.8 (CH₂), 64.11, 64.12 (2xCH₂O), 76.4 (CH-OH), 173.86, 173.91 (2xC=O), 214.5 (-C=O); **HRMS-ESI**: calculated for [M+H]⁺, C₂₆H₄₉O₆: 457.3524, found 457.3521.

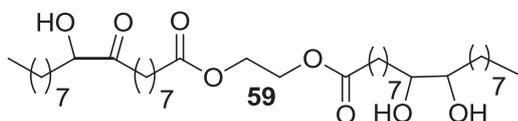
EXPERIMENTAL SECTION



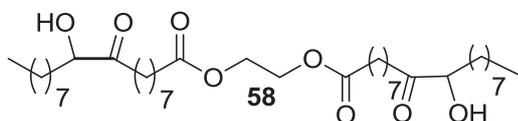
A green oil; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.85\text{-}0.91$ (m, 12H, $4\times\text{CH}_3$), 1.22-1.87 (m, 40H, $19\times\text{CH}_2+2\times\text{CH}$), 2.29 (t, $J=7.5$, 4H, $2\times\text{CH}_2\text{C=O}$), 2.44 (m, 2H, $\text{CH}_2\text{-C=O}$), 2.71 (br s, O-H), 3.97 (dd, $J=5.8, 0.8$, 4H, $2\times\text{OCH}_2$), 4.14 (dd, $J=7.2, 3.6$, 1H, CH-OH); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 11.1$ ($2\times\text{CH}_3$), 14.1 ($2\times\text{CH}_3$), 23.1 ($2\times\text{CH}_2$), 23.6 (CH_2), 23.9 ($2\times\text{CH}_2$), 24.9, 25.0, 25.1 ($3\times\text{CH}_2$), 29.0 ($4\times\text{CH}_2$), 29.10 (CH_2), 29.12 (CH_2), 29.2, 29.4 ($2\times\text{CH}_2$), 30.5 ($2\times\text{CH}_2$), 33.8 (CH_2), 34.4, 34.5 ($2\times\text{CH}_2$), 37.9 (CH_2), 38.8 ($2\times\text{CH}$), 66.7 ($2\times\text{OCH}_2$), 76.4 (CH-OH), 174.07, 174.12 ($2\times\text{C=O}$ ester), 212.5 (C=O ketone); **HRMS-ESI**: calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{34}\text{H}_{65}\text{O}_6$: 569.4776, found 569.4775.



A green solid; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 1.20\text{-}1.80$ (m, 38H, $19\times\text{CH}_2$), 2.29 (t, $J=7.5$, 4H, $2\times\text{CH}_2\text{C=O}$), 2.37-2.51 (m, 2H, $\text{CH}_2\text{-C=O}$), 3.66 (s, 6H, $2\times\text{CH}_3\text{O}$), 4.15 (dd, $J=7.1, 3.6$, CH-OH); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 23.7$, 24.9 ($2\times\text{CH}_2$), 25.0 ($2\times\text{CH}_2$), 29.2 ($2\times\text{CH}_2$), 29.3 ($3\times\text{CH}_2$), 29.4 (CH_2), 29.48 ($3\times\text{CH}_2$), 29.50 (CH_2), 29.54 ($2\times\text{CH}_2$), 29.57 (CH_2), 29.60 (CH_2), 33.9 (CH_2), 34.1 ($2\times\text{CH}_2$), 37.9 (CH_2), 51.5 ($2\times\text{CH}_3\text{O}$), 76.5 (CH-OH), 174.40 ($2\times\text{C=O}$ ester), 212.6 (C=O ketone); **HRMS-ESI**: calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{28}\text{H}_{53}\text{O}_6$: 485.3837, found 485.3835.

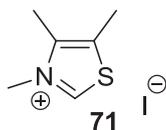


A white solid; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.87$ (t, $J=6.7$, 6H, $2\times\text{CH}_3$), 1.18-1.85 (m, 48H, $24\times\text{CH}_2$), 2.31 (t, $J=7.5$, 4H, $2\times\text{CH}_2\text{C=O}$), 2.40-2.52 (m, 2H, $\text{CH}_2\text{-C=O}$), 3.35-3.45 (m, 2H, $2\times\text{CH}$ -diol), 3.49 (br s, O-H- α -ketol), 4.10-4.18 (m, 1H, C-H- α -ketol), 4.26 (s, 4H, $2\times\text{CH}_2\text{O}$).

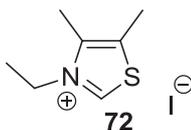


A white solid; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.87$ (t, $J=6.7$, 6H, $2\times\text{CH}_3$), 1.25-1.65 (m, 48H, $24\times\text{CH}_2$), 2.31 (t, $J=7.5$, 4H, $2\times\text{CH}_2\text{C=O}$), 2.41-2.55 (m, 4H, $2\times\text{CH}_2\text{C=O}$), 3.48 (br s, 2H, $2\times\text{O-H}$), 4.10-4.19 (m, 2H, $2\times\text{CH-OH}$), 4.26 (s, $2\times\text{CH}_2\text{O}$); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 14.1$ ($2\times\text{CH}_3$), 22.5, 23.6, 23.7, 24.80, 24.86, 24.89, 28.9, 29.01, 29.04, 29.06, 29.14, 29.26, 29.28, 29.30, 29.35, 29.47, 29.51, 31.8, 31.9, 33.7, 33.8, 34.0, 34.1, 37.8, 37.9 ($26\times\text{CH}_2$), 62.1 ($2\times\text{CH}_2\text{O}$), 76.4, 76.5 ($2\times\text{CH}$), 173.5 ($2\times\text{C=O}_{\text{ester}}$), 212.5, 212.6 ($2\times\text{C=O}_{\text{ketone}}$); **HRMS-ESI**: calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{38}\text{H}_{71}\text{O}_8$: 655.5143, found 655.5120.

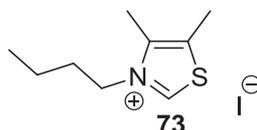
6. Preparation of thiazolium salts.



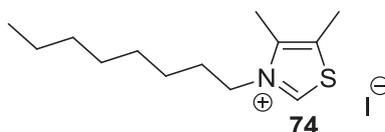
A white solid (mp = 226 °C). **¹H NMR** (300 MHz, CDCl₃): δ_H = 2.50 (s, 3H), 2.53 (s, 3H), 4.38 (s, 3H), 11.03 (s, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ_C = 12.5 (CH₃), 13.1 (CH₃), 42.0 (CH₃), 132.8 (Cq), 142.4 (Cq), 156.5 (CH); **IR** (ν_{max}): 3007, 2966, 2946, 2545, 2168, 1660 (C=N), 1596, 1476, 1443, 1432, 1400, 1392, 1382, 1255, 1188, 1110, 1066, 1050, 1031, 960, 914, 833, 815; **MS** (ESI⁺) m/z = 128.1 ([C₆H₁₀NS]⁺, 100), 382.8 ([2^{*}C₆H₁₀NS⁺, I]⁺, 9); **HRMS** (ESI⁺) [M]⁺ C₆H₁₀NS⁺: requires 128.0528, found 128.0527 (0.9 ppm) and [2M⁺, I]⁺ 2xC₆H₁₀NS⁺, I⁻: requires 383.0107, found 383.0121 (-3.6 ppm).



A white solid (mp: 130-132 °C). **¹H NMR** (300 MHz, CDCl₃): δ_H = 1.66 (t, J=7.3, 3H), 2.49 (s, 3H), 2.56 (s, 3H), 4.73 (q, J=7.3, 2H), 10.97 (s, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ_C = 12.3 (CH₃), 13.2 (CH₃), 15.3 (CH₃), 49.7 (CH₂), 133.3 (Cq), 141.6 (Cq), 155.1 (CH); **IR** ν_{max} = 3008, 2991, 2970, 1587(C=N), 1477, 1435, 1188, 1120, 1097, 1058; **MS** (ESI⁺) m/z = 142.1 ([C₇H₁₂NS]⁺, 100), 411 ([2 x C₇H₁₂NS⁺ + I]⁺, 16); **HRMS** (ESI⁺) [C₇H₁₂NS]⁺ requires 142.0685, found 142.0685 (0 ppm) and [2 x (C₇H₁₂NS)⁺ + I]⁺ requires 411.0420, found 411.0407 (3.1 ppm).



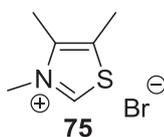
A sand solid (mp = 76 °C). **¹H NMR** (300 MHz, CDCl₃): δ_H = 0.93 (t, J=7.3, 3H), 1.46 (hex, J=7.5, 2H), 1.87 (qt, J=7.7, 2H), 2.50 (s, 3H), 2.54 (s, 3H), 4.61 (t, J=7.6, 2H), 10.72 (s, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ_C = 12.4 (CH₃), 13.2 (CH₃), 13.6 (CH₃), 19.5 (CH₂), 31.8 (CH₂), 54.0 (CH₂), 133.3 (Cq), 141.6 (Cq), 155.8 (CH); **IR** (ν_{max}): 3005, 2955, 2919, 2852, 1587 (C=N), 1467, 1432, 1374, 1352, 1262, 1201, 1187, 1135, 1114, 1072; **MS** (ESI⁺): m/z = 170.1 ([C₉H₁₆NS]⁺, 100); **HRMS** (ESI⁺): [C₉H₁₆NS]⁺ requires 170.0998, found 170.1000 (-0.9 ppm) and [2 x C₉H₁₆NS⁺ + I]⁺ requires 467.1046, found 467.1027 (4.2 ppm).



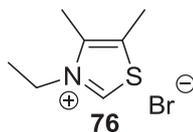
A brown solid (mp = 64°C). **¹H NMR** (300 MHz, CDCl₃): δ_H = 0.75 (t, J=7.0, 3H), 1.04-1.42 (m, 10H), 1.83 (qt, J=7.5, 2H), 2.45 (s, 3H), 2.50 (s, 3H), 4.54 (t, J=7.5, 2H), 10.64 (s, 1H); **¹³C NMR**

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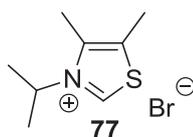
(75 MHz, CDCl₃): δ_c = 12.3 (CH₃), 13.2 (CH₃), 13.9 (CH₃), 22.4 (CH₂), 26.0 (CH₂), 28.78 (CH₂), 28.80 (CH₂), 29.8 (CH₂), 31.5 (CH₂), 54.1 (CH₂), 133.2 (Cq), 141.5 (Cq), 155.6 (CH); **IR** ν_{\max} : 3057, 2950, 2903, 2870, 1588, 1432, 1389, 1378, 1339, 1263, 1241, 1180, 1129, 1065, 1026; **HRMS** (ESI⁺) [M]⁺ C₁₃H₂₄NS⁺ requires 226.1624, found 226.1634 (-4.3 ppm) and [2M⁺, I]⁺ 2 x C₁₃H₂₄NS⁺, I⁻ requires 579.2298, found 579.2301 (-0.4 ppm).



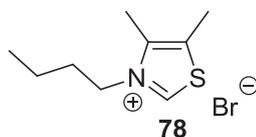
¹H NMR (300 MHz, CDCl₃): δ_H = 2.41 (s, 6H), 4.25 (s, 3H), 10.90 (s, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ_c = 12.0 (CH₃), 12.7 (CH₃), 41.2 (CH₃), 132.4 (Cq), 142.0 (Cq), 156.3 (CH); **IR** ν_{\max} = 2966, 2946, 1660 (C=N), 1596, 1188, 1110, 1066, 1050; **MS** (ESI⁺) m/z = 128.1 ([C₆H₁₀NS]⁺, 100), 335.0 ([2 x C₆H₁₀NS⁺ + Br⁻]⁺, 48); **HRMS** (ESI⁺) [C₆H₁₀NS]⁺ requires 128.0528, found 128.0526 (1.7 ppm) and [2 x (C₆H₁₀NS)⁺ + Br⁻]⁺ requires 335.0246, found 335.0242 (1.0 ppm).



A white solid (mp = 178-182 °C). **¹H NMR** (300 MHz, CDCl₃): δ_H = 1.55 (t, *J*=7.3, 3H), 2.45 (s, 3H), 2.46 (s, 3H), 4.65 (q, *J* = 7.2, 2H), 11.04 (s, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ_c = 11.8 (CH₃), 12.8 (CH₃), 15.4 (CH₃), 49.4 (CH₂), 133.2 (Cq), 141.3 (Cq), 156.1 (CH); **IR** ν_{\max} = 2933, 2897, 1593 (C=N), 1577, 1440, 1402, 1174, 1136, 1101, 1064; **MS** (ESI⁺) m/z = 142.1 ([C₇H₁₂NS]⁺, 100), 363.1 ([2 x C₇H₁₂NS⁺ + I⁻]⁺, 43); **HRMS** (ESI⁺) [C₇H₁₂NS]⁺ requires 142.0685, found 142.0688 (-1.9 ppm) and [2 x (C₇H₁₂NS)⁺ + I⁻]⁺ requires 363.0559, found 363.0557 (0.5 ppm).

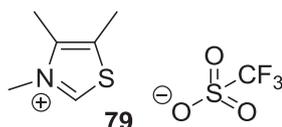


A white solid (mp = 169-171 °C). **¹H NMR** (300 MHz, CDCl₃): δ_H = 1.64 (d, *J*=6.7, 6H), 2.47 (s, 3H), 2.49 (s, 3H), 4.89 (sept, *J*=6.7, 1H), 10.89 (s, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ_c = 12.3 (CH₃), 12.8 (CH₃), 22.9 (2 CH₃), 57.0 (CH), 133.3 (Cq), 141.2 (Cq), 155.3 (CH); **IR** ν_{\max} = 2940, 1588 (C=N), 1452, 1243, 1196, 1138, 1123, 1041; **MS** (ESI⁺) m/z = 156.1 ([C₈H₁₄NS]⁺, 100), 391.1 ([2 x C₈H₁₄NS⁺ + Br⁻]⁺, 33); **HRMS** (ESI⁺) [C₈H₁₄NS]⁺ requires 156.0841, found 156.0838 (2 ppm) and [2 x (C₈H₁₄NS)⁺ + Br⁻]⁺ requires 391.0872, found 391.0861 (2.8 ppm).

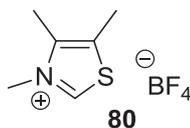


EXPERIMENTAL SECTION

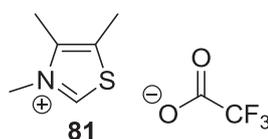
A sandy solid (mp = 45-50°C). $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} = 0.79 (t, $J=7.4$, 3H), 1.28 (hex, $J=7.4$, 2H), 1.73 (qt, $J=5.5$, 2H), 2.38 (s, 3H), 2.42 (s, 3H), 4.53 (t, $J=7.6$, 2H), 10.93 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ_{C} = 11.8 (CH₃), 12.7 (CH₃), 13.3 (CH₃), 19.2 (CH₂), 31.6 (CH₂), 53.5 (CH₂), 133.0 (Cq), 141.1 (Cq), 156.3 (CH); IR (ν_{max}): 2929, 2870, 1588 (C=N), 1442, 1218, 1115; MS (ESI⁺): m/z = 170.1 ([C₉H₁₆NS⁺], 100), 419.1 ([2 x C₉H₁₆NS⁺ + Br⁻]⁺, 11); HRMS (ESI⁺): [C₉H₁₆NS]⁺ requires 170.0998, found 170.0992 (3.6 ppm), [2 x C₉H₁₆NS⁺ + Br⁻]⁺ requires 419.1185 found 419.1165 (4.8 ppm).



A white solid (mp = 220-226°C). $^1\text{H NMR}$ (400 MHz, d_6 -DMSO): δ_{H} = 2.40 (s, 3H), 2.49 (s, 3H), 4.07 (s, 3H), 9.91 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, d_6 -DMSO): δ_{C} = 10.9 (CH₃), 11.8 (CH₃), 40.2 (CH₃), 120.7 (CF₃, q, $^1J_{\text{C-F}}$ = 318), 132.3 (Cq), 142.2 (Cq), 155.7 (CH); $^{19}\text{F NMR}$ (376 MHz, d_6 -DMSO): δ_{F} = -78.55 (CF₃); IR ν_{max} = 3529, 3078, 3066, 2987, 1598 (C=N), 1485, 1444, 1411, 1149, 1111, 1029; MS (ESI⁺) m/z = 128.1 ([C₆H₁₀NS⁺], 100), 382.8 ([2 C₆H₁₀NS⁺ + OTf⁻]⁺, 60); HRMS (ESI⁺) [C₆H₁₀NS]⁺ requires 128.0528, found 128.0528 (0.0 ppm) and [2 (C₆H₁₀NS)⁺ + OTf⁻]⁺ requires 405.0583, found 405.0575 (2.0 ppm).

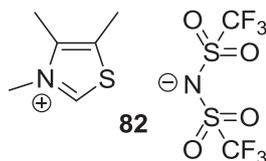


A sandy solid (mp = 158-162°C). $^1\text{H NMR}$ (400 MHz, d_6 -DMSO): δ_{H} = 2.39 (s, 3H), 2.48 (s, 3H), 4.06 (s, 3H), 9.90 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, d_6 -DMSO): δ_{C} = 11.3 (CH₃), 12.3 (CH₃), 40.6 (CH₃), 132.8 (Cq), 142.6 (Cq), 156.1 (CH); $^{19}\text{F NMR}$ (376 MHz, d_6 -DMSO): δ_{F} = -148.26 (BF₄); IR (ν_{max}): 3115, 1601 (C=N), 1021; MS (ESI⁺): m/z = 128.1 ([C₆H₁₀NS]⁺, 100), 343.1 ([2 C₆H₁₀NS⁺ + BF₄⁻]⁺, 13); HRMS (ESI⁺): [C₆H₁₀NS]⁺ requires 128.0528, found 128.0533 (-3.2 ppm) and [2 C₆H₁₀NS⁺ + BF₄⁻]⁺ requires 343.1094, found 343.1140 (-3.6 ppm).

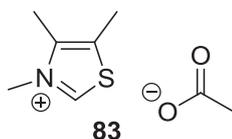


A white solid (mp = 94-96°C). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ_{H} = 2.47 (s, 3H), 2.52 (s, 3H), 4.25 (s, 3H), 11.22 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ_{C} = 11.0 (CH₃), 12.1 (CH₃), 40.3 (CH₃), 116.9 (CF₃, q, $^1J_{\text{C-F}}$ = 295), 132.5 (Cq), 141.8 (Cq), 156.7 (CH), 160.5 (C=O, q, $^2J_{\text{C-F}}$ = 32); $^{19}\text{F NMR}$ (282 MHz, CDCl_3): δ_{F} = -75.28 (CF₃); IR (ν_{max}): 3115, 2994, 2935, 1679 (C=O), 1599 (C=N), 1488, 1404, 1195, 1110; MS (ESI⁺): m/z = 128.1 ([C₆H₁₀NS]⁺, 100), 369.1 ([2 C₆H₁₀NS + CF₃COO⁻]⁺, 27); HRMS (ESI⁺): [2 C₆H₁₀NS⁺ + CF₃COO⁻]⁺ requires 369.0913, found 369.0901 (3.1 ppm).

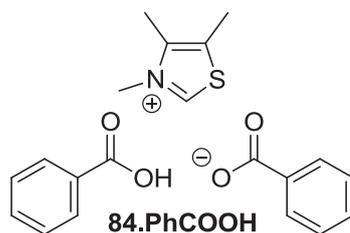
EXPERIMENTAL SECTION



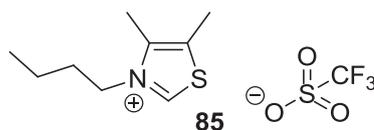
A sandy solid (mp = 255-258 °C). $^1\text{H NMR}$ (400 MHz, d_6 -DMSO): δ_{H} = 2.40 (s, 3H), 2.49 (s, 3H), 4.08 (s, 3H), 9.94 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, d_6 -DMSO): δ_{C} = 11.1 (CH₃), 12.0 (CH₃), 40.4 (CH₃), 119.7 (2 CF₃, q, $^1J_{\text{C-F}}$ = 278), 132.3 (Cq), 142.2 (Cq), 155.6 (CH); $^{19}\text{F NMR}$ (376 MHz, d_6 -DMSO): δ_{F} = -78.8 (2 CF₃); IR ν_{max} = 3402, 3007, 1597 (C=N), 1477, 1447, 1186, 1136, 1109, 1051, 1033;; **MS** (ESI⁺): m/z = 128.05 ([C₆H₁₀NS]⁺, 100), 536.02 ([2 C₆H₁₀NS + NTf₂⁻]⁺, 88); **HRMS** (ESI⁺): [C₆H₁₀F₃NS]⁺ requires 128.0528, found 128.0532 (-2.5 ppm), [2 C₆H₁₀NS + NTf₂⁻]⁺, requires 536.0235, found 536.0230 (1.0 ppm).



The compound was prepared following standard procedures but was found instable. As a result, it was prepared in D₂O for characterization purposes. $^1\text{H NMR}$ (300 MHz, D₂O): δ_{H} = 1.90 (s, 3H), 2.42 (s, 3H), 2.50 (s, 3H), 4.06 (s, 3H).



A white solid (mp = 141-145°C). $^1\text{H NMR}$ (400 MHz, d_6 -DMSO): δ_{H} = 2.33 (s, 3H), 2.41 (s, 3H), 4.07 (s, 3H), 7.16-7.60 (m, 6H), 7.70-8.25 (m, 4H), 10.22 (s, 1H), 11.96 (br s, 1H); $^{13}\text{C NMR}$ (100 MHz, d_6 -DMSO): δ_{C} = 10.8 (CH₃), 11.8 (CH₃), 40.2 (CH₃), 127.9 (4 CH), 129.1 (4 CH), 131.1 (2 CH), 132.2 (Cq), 134.8 (2 Cq), 142.0 (Cq), 156.0 (CH), 168.3 (2 C=O); IR ν_{max} = 3030, 2987, 2960, 2933, 1641, 1629 (C=N), 1573, 1261, 1197, 1066, 1188, 1110, 1066, 1050; **MS** (ESI⁺): m/z = 128.1 [C₆H₁₀NS]⁺; (ESI⁻): m/z = 121.0 [PhCO₂]⁻; **HRMS** (ESI⁺): [C₆H₁₀NS]⁺ requires 128.0528, found 128.0530 (-1.5 ppm).

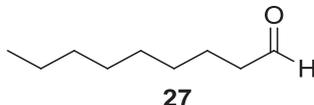


A colourless oil. ^1H (300 MHz, CDCl₃): δ_{H} = 0.97 (t, J =7.3, 3H), 1.42 (hex, J =7.3, 2H), 1.77-1.93 (m, 2H), 2.47 (s, 3H), 2.53 (s, 3H), 4.44 (t, J =7.5, 2H), 9.97 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl₃): δ_{C} = 11.5 (CH₃), 12.6 (CH₃), 13.4 (CH₃), 19.4 (CH₂), 31.5 (CH₂), 53.9 (CH₂-N), 133.6 (Cq), 141.7

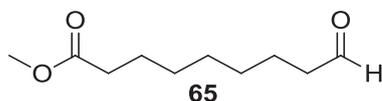
EXPERIMENTAL SECTION

(Cq), 154.7 (CH); HRMS (ESI⁺): [C₉H₁₆NS]⁺ requires 170.0998, found 170.0986, [(2 C₉H₁₆NS⁺ + O₃SCF₃⁻)⁺ requires 489.1, found 489.1.

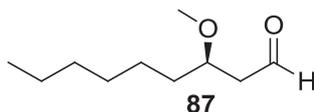
7. Characterisation of aldehydes



A colourless oil. **IR** (ν_{\max}): 2923, 2854, 2359, 2025, 1707 (C=O), 1458, 1412, 1287, 1222, 1146, 1113, 938, 722; **¹H NMR** (300 MHz, CDCl₃): δ_{H} = 0.84 (t, J =6.4, 3H, CH₃), 1.10-1.40 (m, 10H, 5 CH₂), 1.50-1.70 (m, 2H, CH₂), 2.37 (tt, J =7.3, 1.5, 2H, CH₂-CHO), 9.72 (t, J =1.8, 1H, CHO); **¹³C NMR** (75 MHz, CDCl₃): δ_{C} = 14.1 (CH₃), 22.1 (CH₂), 22.7 (CH₂), 29.1 (CH₂), 29.2 (CH₂), 29.4 (CH₂), 31.9 (CH₂), 44.0 (CH₂), 203.0 (C=O).

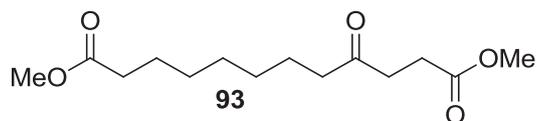


A yellowish oil. **IR** (ν_{\max}): 2929, 2856, 2359, 1736 (C=O), 1706 (C=O), 1436, 1414, 1196, 1170, 1097, 1011, 940, 899, 726; **¹H NMR** (300 MHz, CDCl₃): δ_{H} = 1.15-1.38 (m, 6H, 3-CH₂); 1.45-1.75 (m, 4H, 2-CH₂), 2.30 (t, J =7.4, 2H, CH₂-C=O), 2.41 (td, J =7.3, 1.8, 2H, CH₂-CHO), 3.65 (s, 3H, OCH₃), 9.75 (t, J =1.8, 1H, CHO); **¹³C NMR** (75 MHz, CDCl₃): δ_{C} = 22.1 (CH₂), 25.0 (CH₂), 29.01 (CH₂), 29.06 (CH₂), 29.1 (CH₂), 34.1 (CH₂), 43.9 (CH₂), 51.6 (CH₃), 174.4 (C=O ester), 202.9 (C=O aldehyde); **MS (ESI⁺)** m/z = 187.0 ([M+H]⁺, 100).



A yellowish liquid. **¹H NMR** (300 MHz, CDCl₃): 0.88 (t, J = 6.7, 3H, CH₃), 1.20-1.65 (m, 10H, 5-CH₂), 2.51 (ddd, J = 16.2, 5.0, 2.0, 1H), 2.60 (ddd, J = 16.2, 7.0, 2.6, 1H), 3.34 (s, 3H, OCH₃), 3.70 (dtd, J = 7.0, 6.0, 5.2, 1H, CH-OMe), 9.80 (dd, J = 2.6, 2.0, CH=O); **¹³C NMR** (75 MHz, CDCl₃): δ_{C} = 14.1 (CH₃), 22.6, 25.0, 29.4, 31.8, 33.9 (5-CH₂), 48.0 (CH₂-C=O), 56.8 (CH₃O), 76.4 (CH-OMe), 201.7 (-C=O); **HRMS-ESI**: calculated for [M+Na]⁺, C₁₀H₂₀O₂Na: 195.1356, found 195.1353.

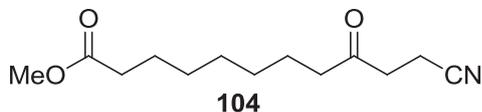
8. Characterisation of Stetter adducts



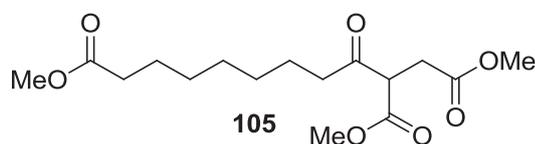
A waxy solid ; **¹H NMR** (300 MHz, CDCl₃): δ_{H} = 1.26-1.35 (6H, m), 1.52-1.68 (4H, m), 2.30 (2H, t, J =7.6, H-3), 2.45 (2H, t, J =7.5, H-9), 2.59 (2H, t, J =6.5, H-12), 2.72 (2H, t, J =6.5, H-11), 3.67

EXPERIMENTAL SECTION

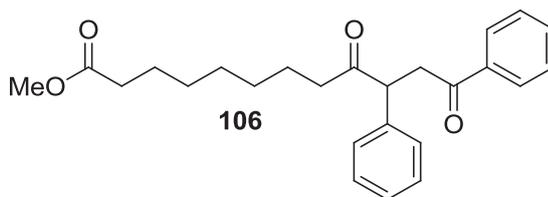
(3H, s, H-1), 3.68 (3H, s, H-14); ^{13}C NMR (75 MHz, CDCl_3): $\delta_{\text{c}} = 23.5$ (CH_2), 24.7 (CH_2), 27.5 (CH_2), 28.8 (2CH_2), 289 (CH_2), 33.9 (CH_2), 42.5 (CH_2), 51.3 (OCH_3), 51.6 (OCH_3), 173.1 ($\text{C}=\text{O}$), 174.1 ($\text{C}=\text{O}$), 208.9 ($\text{C}=\text{O}$); HRMS (ESI^+) $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{24}\text{NaO}_5$: requires 295.1516, found 295.1510 (2.0 ppm).



A white solid ; ^1H NMR (300 MHz, CDCl_3): $\delta_{\text{H}} = 1.25$ -1.36 (6H, m), 1.54-1.68 (4H, m), 2.31 (2H, t, $J=7.4$), 2.45 (2H, t, $J=7.5$), 2.59 (2H, t, $J=7.1$), 2.80 (2H, t, $J=7.1$), 3.67 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): $\delta_{\text{c}} = 11.2$ (CH_2), 23.4 (CH_2), 24.6 (CH_2), 28.7 (2xCH_2), 28.8 (CH_2), 33.8 (CH_2), 37.5 (CH_2), 42.2 (CH_2), 51.3 (OCH_3), 119.0 (CN), 174.0 ($\text{C}=\text{O}$), 206.2 ($\text{C}=\text{O}$); HRMS (ESI^+) $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{21}\text{NNaO}_3$: requires 262.1414, found 262.1419 (2.1 ppm).

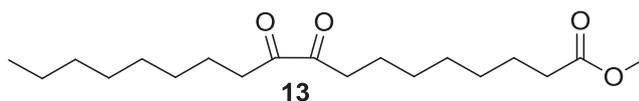


A white solid ; ^1H NMR (300 MHz, CDCl_3): $\delta_{\text{H}} = 1.24$ -1.36 (6H, m), 1.52-1.70 (4H, m), 2.30 (2H, t, $J=7.4$), 2.55-2.77 (2H, m), 2.84 (1H, dd, $J=17.6$, 6.3), 2.99 (1H, dd, $J=17.6$, 8.2), 3.67 (3H, s), 3.68 (3H, s), 3.75 (3H, s), 3.99 (1H, dd, $J=8.2$, 6.3); ^{13}C NMR (75 MHz, CDCl_3): $\delta_{\text{c}} = 23.0$ (CH_2), 24.6 (CH_2), 28.5 (CH_2), 28.68 (CH_2), 28.74 (CH_2), 31.9 (CH_2), 33.8 (CH_2), 42.4 (CH_2), 51.2 (OCH_3), 51.8 (OCH_3), 52.5, 53.5, 168.7 ($\text{C}=\text{O}$), 171.6 ($\text{C}=\text{O}$), 173.9 ($\text{C}=\text{O}$), 203.6 ($\text{C}=\text{O}_{\text{ketone}}$); HRMS (ESI^+) $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{27}\text{O}_7$: requires 331.1751, found 331.1745 (1.9 ppm).

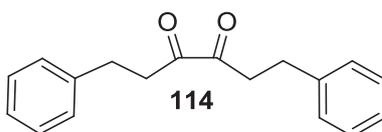


A white solid ; ^1H NMR (300 MHz, CDCl_3): $\delta_{\text{H}} = 1.12$ -1.30 (6H, m), 1.44-1.66 (m, 4H), 2.26 (2H, t, $J=7.4$), 2.40-2.51 (1H, m), 2.55-2.66 (1H, m), 3.11 (1H, dd, $J=18.1$, 3.7), 3.65 (3H, s), 4.03 (1H, dd, $J=18.0$, 10.2), 4.41 (1H, dd, $J=10.2$, 3.6), 7.25-7.30 (3H, m), 7.31-7.38 (2H, m), 7.40-7.47 (2H, m), 7.51-7.58 (1H, m), 7.92-7.98 (2H, m); ^{13}C NMR (75 MHz, CDCl_3): $\delta_{\text{c}} = 23.6$, 24.9, 28.8, 29.0, 34.1, 41.8, 42.4 (8 CH_2), 51.5 (CH_3O), 53.4 (CH), 127.6, 128.2, 128.4, 128.6, 129.2, 133.2 (10 CH aromatic), 136.6, 138.3 (2 C aromatic), 174.3 ($\text{C}=\text{O}$ ester), 198.3 ($\text{C}=\text{O}$ ketone), 209.4 ($\text{C}=\text{O}$ ketone); HRMS (ESI^+) $[\text{M}+\text{H}]^+$ $\text{C}_{25}\text{H}_{31}\text{O}_4$: requires 395.2217, found 395.2214 (0.6 ppm).

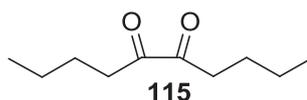
9. Characterisation of fatty diketones and their cleavage products



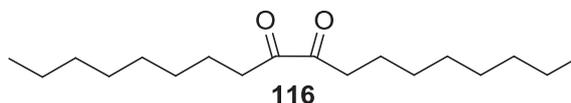
A green solid ; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.87$ (t, $J = 6.7$, 3H, CH_3), 1.26-1.30 (m, 16H, 8 CH_2), 1.53-1.60 (m, 6H, 3 $\times\text{CH}_2$), 2.29 (t, $J = 7.5$, 2H, 2 CH_2), 2.72 (t, $J = 7.3$, 4H, 2 $\times\text{CH}_2$), 3.65 (s, 3H, OCH_3); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 12.5$ (CH_3), 22.9, 23.2, 23.4, 25.1, 27.4, 29.2, 29.2, 29.3, 29.4, 29.6, 32.1, 33.6, 34.6, 36.3, 36.3 (15- CH_2), 51.8 (OCH_3), 174.4 ($\text{C}=\text{O}$ ester), 200.3, 200.4 (2 $\text{C}=\text{O}$).



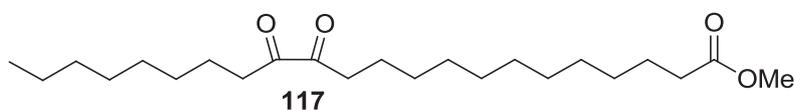
A yellow solid (mp = 86-88°C); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 2.89$ (t, $J = 7.1$, 4H), 3.06 (t, $J = 7.1$, 4H, 2 CH_2), 7.20 - 7.40 (m, 10H, 10 CH aromatic).



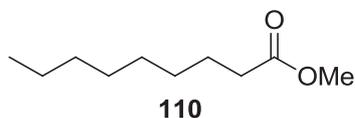
A yellow oil; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.93$ (t, $J = 7.3$, 6H, 2 $\times\text{CH}_3$), 1.36 (dd, $J = 15.0$, 7.4, 4H, 2 $\times\text{CH}_2$), 1.55 (dd, $J = 11.1$, 4.0, 4H, 2 $\times\text{CH}_2$), 2.75 (t, $J = 7.4$, 4H, 2 $\times\text{CH}_2$).



A yellow solid (mp = 59-61°C); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.88$ (t, $J = 6.7$, 6H, 2 $\times\text{CH}_3$), 1.23 - 1.37 (m, 20H, 10 $\times\text{CH}_2$), 1.55-1.67 (m, 4H, 2 $\times\text{CH}_2$), 2.72 (t, $J = 7.4$, 4H, 2 $\times\text{CH}_2$).

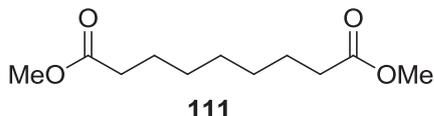


A green solid; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.87$ (t, $J = 6.7$, 3H, CH_3), 1.20-1.35 (m, 24H, 12 $\times\text{CH}_2$), 1.50-1.64 (m, 6H, 3 $\times\text{CH}_2$), 2.29 (t, $J = 7.5$, 2H, 2 CH_2), 2.71 (t, $J = 7.3$, 4H, 2 $\times\text{CH}_2$), 3.65 (s, 3H, OCH_3); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 14.2$ (CH_3), 22.7, 23.2, 25.1, 29.2, 29.3, 29.4, 29.41, 29.42, 29.50, 29.51, 29.6, 31.9, 34.2, 36.2 (18 $\times\text{CH}_2$), 51.4 (OCH_3), 174.4 ($\text{C}=\text{O}$ ester), 200.3 (2 $\times\text{C}=\text{O}_{\text{ketone}}$).



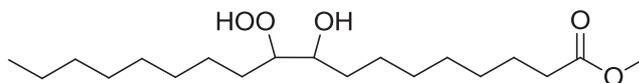
EXPERIMENTAL SECTION

A colourless liquid; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 0.87$ (t, $J = 6.7$, 3H, CH_3), 1.17 – 1.34 (m, 10H, $5 \times \text{CH}_2$), 1.60 (dd, $J = 14.7, 7.3$, 2H, CH_2), 2.29 (t, $J = 7.5$, 2H), 3.65 (s, 3H, CH_3).



A colourless liquid; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta_{\text{H}} = 1.19$ -1.31 (m, 6H, $3 \times \text{CH}_2$), 1.51-1.60 (m, 4H, 2 CH_2), 2.25 (t, $J = 7.5$, 4H, $2 \times \text{CH}_2$), 3.61 (s, 6H, $2 \times \text{CH}_3\text{O}$).

10. Characterisation of fatty β -hydroxy hydroperoxide



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A colourless liquid; $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$): $\delta_{\text{H}} = 0.85$ (t, $J = 6.7$, 3H, CH_3), 1.20-1.61 (m, 26H, $13 \times \text{CH}_2$), 2.27 (t, $J = 7.5$, 2H, $\text{CH}_2\text{-C=O}$), 3.58 (s, 3H, OCH_3), 3.50-3.62 (m, 2H, CH), 4.33 (dd, $J = 5.2, 2.0$, 1H, O-H), 11.1 (d, $J = 1.2$, 1H, O-OH); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta_{\text{C}} = 13.9$ (CH_3), 22.6, 24.8, 25.3, 25.5, 28.6, 29.0, 29.1, 29.3, 29.4, 29.5, 29.7, 31.9, 33.1, 34.1 (14-CH_2), 51.5 (OCH_3), 72.9 (CH-OH), 87.9 (CH-OOH), 174.6 (C=O).

LIST OF PUBLICATIONS

1. Nam Duc Vu, Boris Guicheret, Nicolas Duguet, Estelle Métay and Marc Lemaire, "Homogeneous and heterogeneous catalytic (dehydrogenative) oxidation of oleochemical 1,2-diols to α -hydroxyketones", *Green Chem.* **2017**, *19*, 3390-3399.
2. Nam Duc Vu, Souleymane Bah, Elsa Deruer, Nicolas Duguet, Marc Lemaire, " Robust Organocatalysts for the Cleavage of Vegetable Oil Derivatives to Aldehydes through Retrobenzoin Condensation", *Chem. Eur. J.* **2018**, *24*, 8141-8150.
3. Kevin Grollier, Nam Duc Vu, Sébastien Norsic, Franck D'Agosto, Christophe Boisson, Nicolas Duguet, "A Thermomorphic Polyethylene-Supported Imidazolium Salt for the Fixation of CO₂ into Cyclic Carbonates", *Green Chem.* **2018**, under revision.
4. Aubin Charvieux, Nam Duc Vu, Nicolas Duguet, Marc Lemaire, "Valorization of methyl azelaaldehyde - a vegetable oil-based platform molecule – to monomers through Stetter reaction", Manuscript on preparation.
5. Nam Duc Vu, Romain Chavallard, Thomas De Dios Miguel, Nicolas Duguet, Marc Lemaire "Oxidative cleavage of fatty 1,2-diketones into esters through organocatalysis", Manuscript on preparation.
6. Benoit Briou, Nam Duc Vu, Sylvain Caillol, Jean-Jacques Robin, Nicolas Duguet, Marc Lemaire, Pascal Etienne, Vincent Lapinte, "Polyurethane thermosets using lipidic poly(α -hydroxyketone), Manuscript on preparation.