Chapter 1

Introduction

L-Proline and Oleochemicals – An Important Renewable Feedstock

1.1 Chemistry: Nobel Prize 2021

The Royal Swedish Academy of Sciences awarded the prestigious Nobel Prize to **Benjamin List** and **David MacMillan**, and applauded their contribution "for the development of asymmetric organocatalysis" (Fig.1).[1]

Fig. 1. Noble laureates Prof. Benjamin List and Prof. David Macmillan.[1]

In the year 2000, List and MacMillan, independent of each other, had developed a third type of catalysis called asymmetric organocatalysis, which based on small organic molecules. They reported potential of an amino acid molecule 'proline' to catalyse chemical transformations.[1]

1.2 Types of Catalysts and Importance of Organocatalysts

"*A catalyst accelerates a chemical reaction without affecting the position of the equilibrium.*" – Ostwald. 'Use of Catalysts' is one of the principle of the well-known twelve principles of Green Chemistry. Catalysts are usually classified according to structure, composition, area of application or state of aggregation (Table 1). Each types of catalysts have importance in their particular domain. Recovery and recycling perspective, organometallic type is widely useful. However, it is not recommended for the products which are going to use for human health directly due to its toxic metal contamination concern. Enzymatic catalysts are very effective for the specific product selectivity purpose. But there are very limited substrate in enzymatic catalysts, hence it is not explored to a wide range of application. Organocatalysts are important to overcome above limitations. It is the area for catalysts to introduce green sourced chemicals for the catalytic purpose which are in alignment of the trends for catalysts in the direction of sustainability.

Table 1. Types of catalysts and its pros and cons.[2]

Organometallic catalyst	Enzyme catalyst	Organocatalyst
• Wide substrate scope • High catalytic activity • Potential heavy metal pollution • Involving tedious process	• High selectivity and catalytic activity • Usually single enantiomer • Limited substrate scope	• Robust • Inexpensive • Readily available • Nontoxic • Inert toward moisture and oxygen • Method especially attractive for the preparation of compound that do not tolerate metal contamination (pharmaceutical products)

1.3 Types of Organocatalysts

In organocatalysts, we have listed out various types likes chiral amines and amides, iminium salts, carbenes derivatives, supramolecular compounds, ionic liquids, photo-organocatalysts and catalysts molecules immobilized on supporting materials like metal oxides or polymeric compounds (Fig. 2).[3]

For the work presented in the thesis, we are mainly interested on chiral amine type catalysts. The thought process to apply L-proline, a chiral cyclic amine and its derivatives as green sourced material, which can effectively work in the aqueous system resulting a specific stereoisomer as a sole product.

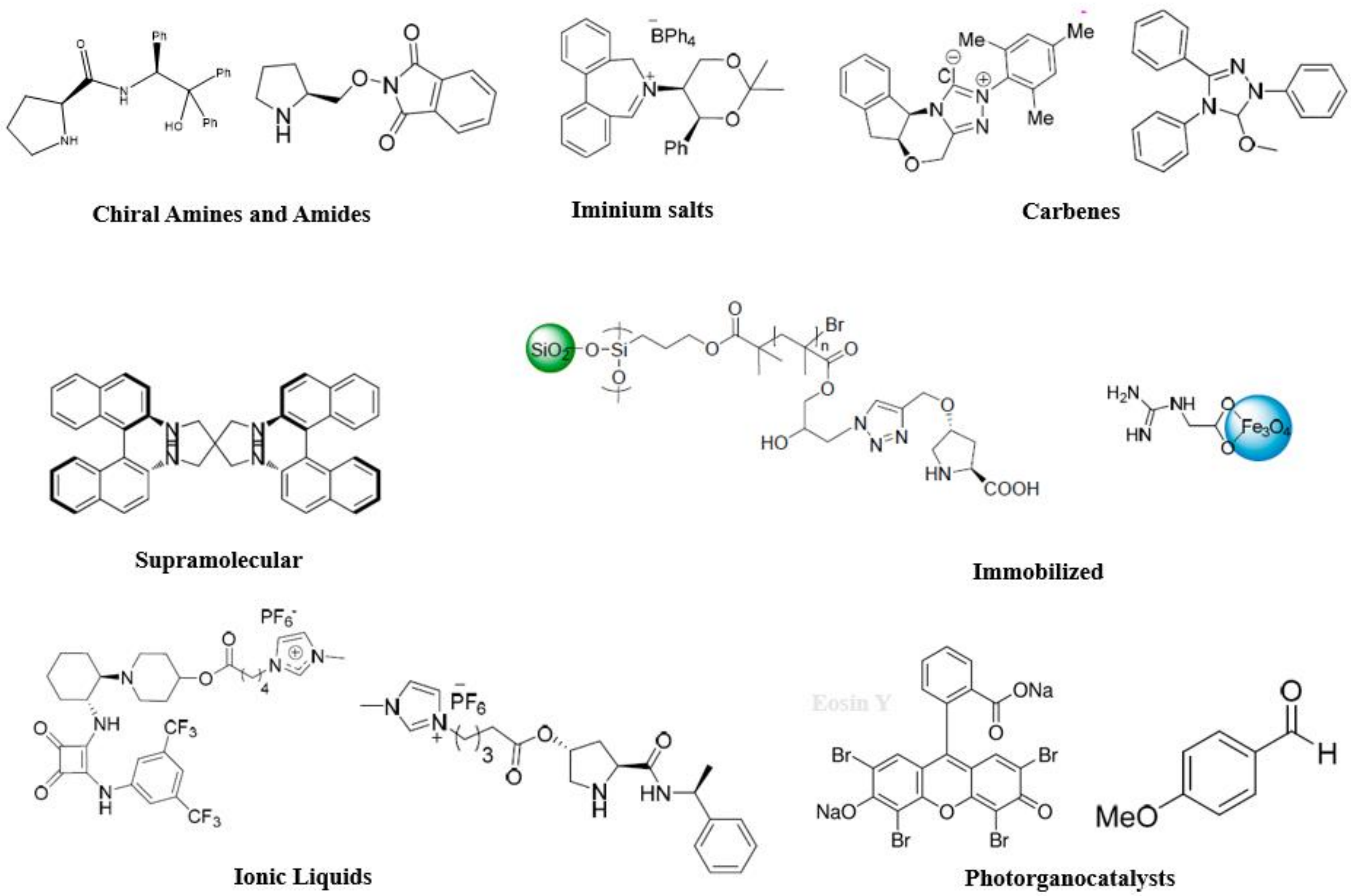

Fig. 2. Types of organocatalysts.[3]

L-proline was first introduced as an organocatalyst for the intra-molecular Aldol reaction by Hajos-Parrish-Eder-Sauer-Wiechert in 1971. Then after L-proline was explored for inter-molecular Aldol reaction by Barbas, Learner and List in 2000. L-proline was reported specifically for enantio-selectivity of cross-Aldol reactions by MacMillan in 2002. In 2007, L-proline was modified to prolinamide derivative by Barbas to make it applicable in aqueous media. In the direction of sustainability, research for organocatalysts has been started since last two decades (Fig. 3). For the purpose, the modified catalyst must be effective in high water content, it can be recyclable and its less loading should be required for the asymmetric organic transformations. The development of catalytic synthetic processes in water is currently one of the frontiers in the research field. The generation of several bonds in a single operation in a multi-component reaction carried out in water is one of the most powerful approaches to sustainable synthesis.[5]

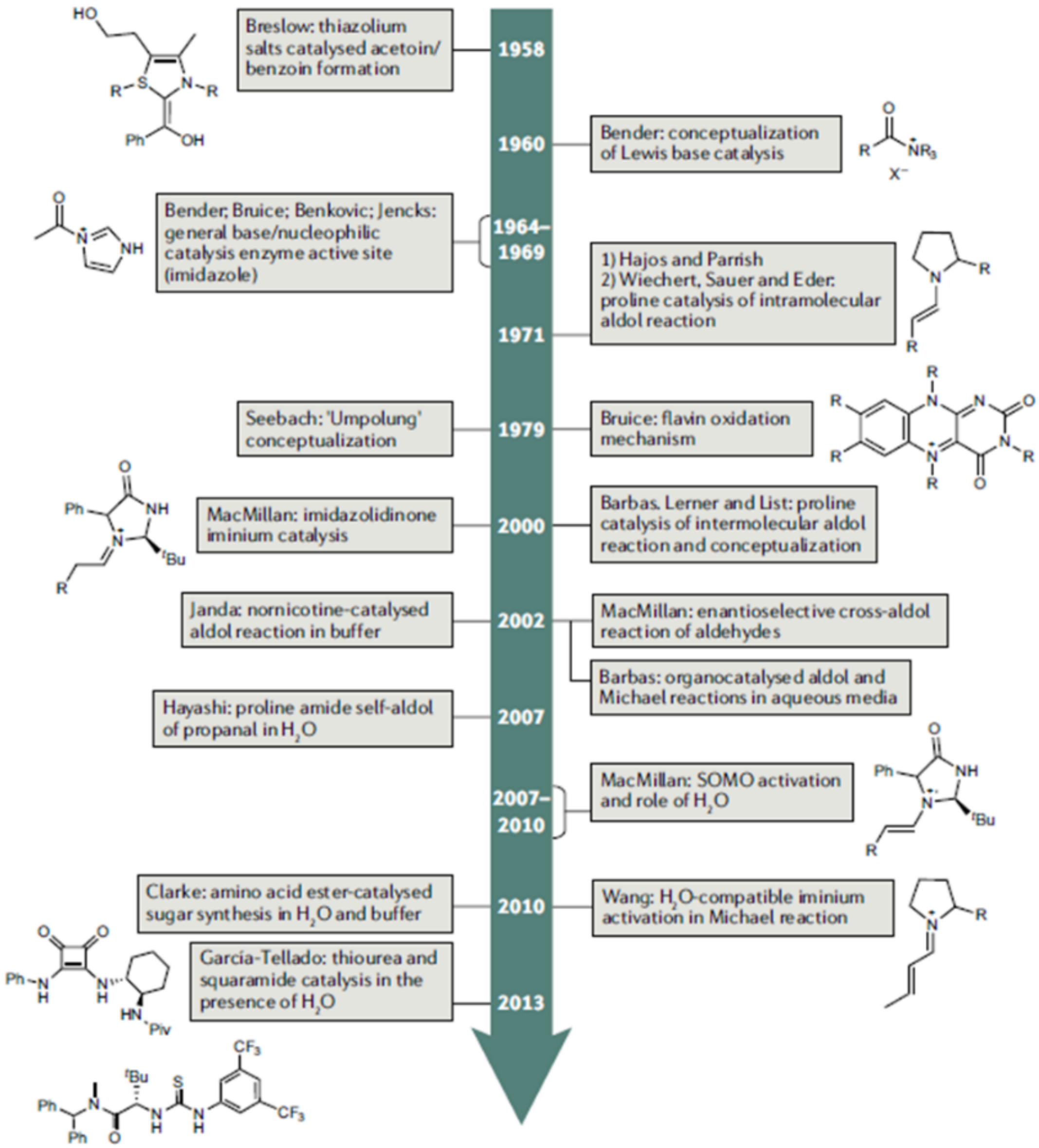

Fig. 3. Trend of organocatalysts.[4]

1.4 Why L-proline is Special?

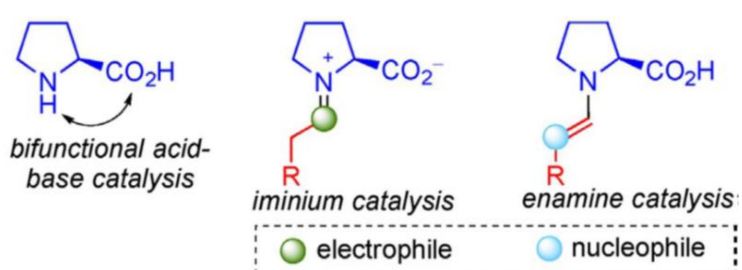

Fig. 4. Bifunctional behaviour of L-proline.[5]

One of the key event in the initial development of organocatalysis was the discovery by List, Lerner and Barbas that L- proline is an excellent catalyst for the direct asymmetric intermolecular Aldol reactions. Among all natural twenty-two amino acids, L-Proline is the only cyclic amino acid with a secondary amine functionality, this feature enhances its nucleophilicity compared to other amino acids. L-proline nitrogen has a reactivity towards carbonyl groups due to its loan pair electron generating the iminium or enamine intermediates that are characteristic of covalent organocatalysis (Fig. 4). The presence of the carboxylic acid functionality allows the formation of organized transition states stabilized by several hydrogen bonds, often leading to high stereoselectivity (Fig. 5).[5]

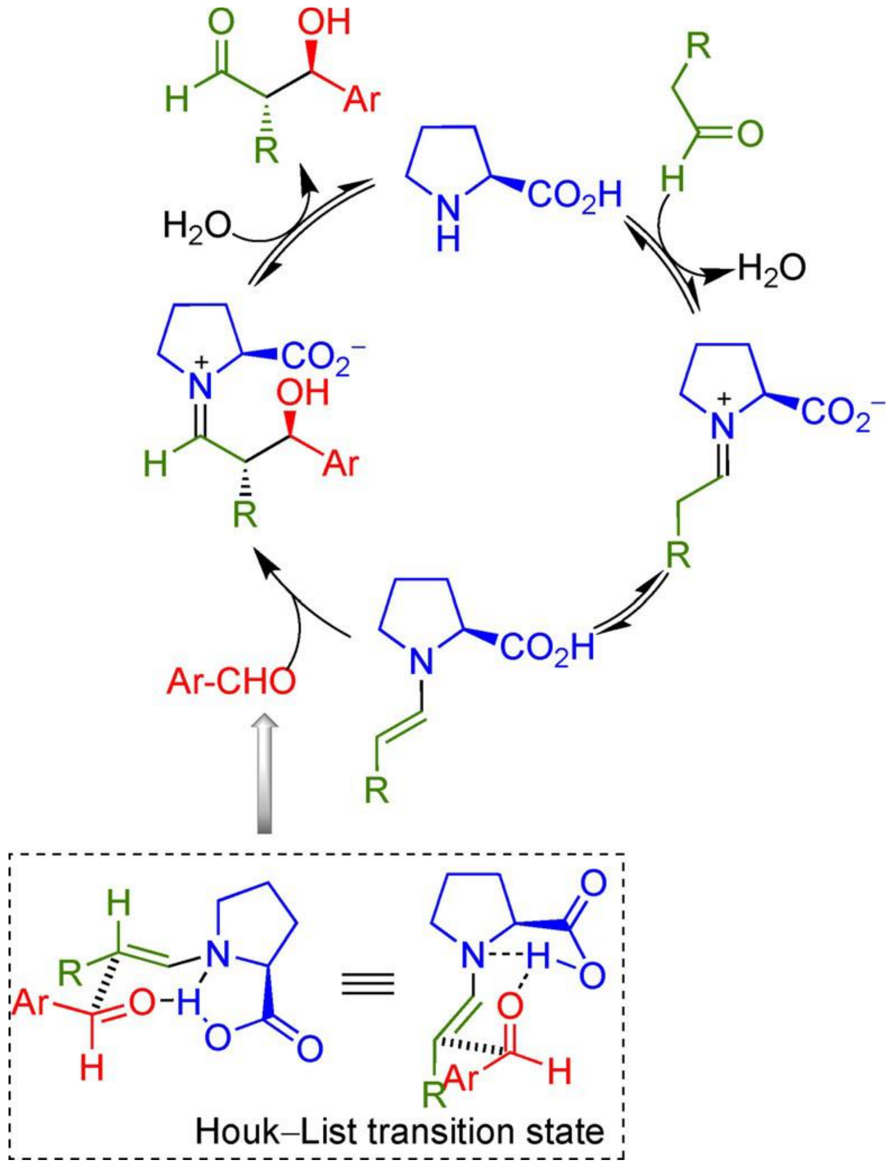

Fig. 5. Mechanism proposed for the proline-catalysed Aldol reaction via enamine catalysis.[5]

1.5 Need of L-proline Modification

(i) Due to insolubility in non-polar solvents, L-proline mediated reactions are carried out in an excess of one of the Aldol substrate (usually donor) as the solvent (ii) large amount (30 mole%) of catalyst loading is required for a single cycle of reaction (iii) the unmodified proline does not catalyse Aldol reaction in water. If the reaction is carried out in water, the enantiomeric induction is hampered.

For a ‘Green chemistry’ perspective, different terminologies are coined when water is involved in an asymmetric reaction like ‘in water’, ‘on water’ and ‘in presence of water’. The term ‘in water’ is used for the reaction having excess amount of water (>100 equivalent of water). ‘On water’ is used for the reactions which are carried out on the surface of water layer or water droplets. ‘In presence of water’ is used for the reactions in which presence of water molecules are playing a role to enhance the reaction or improve the selectivity of the products.

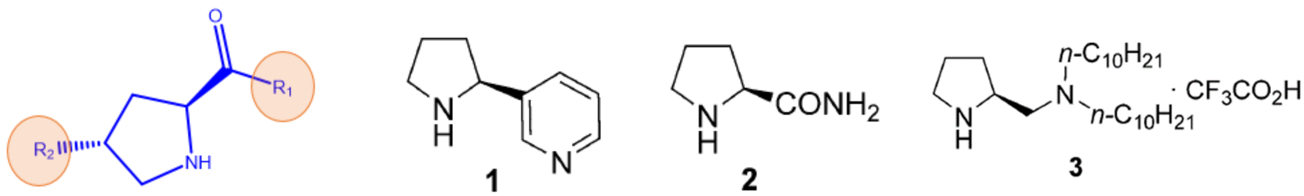

Fig. 6. Preferred modification sites of L-proline and structures (**1**, **2** and **3**) of the first proline-related compound used to catalyse Aldol reactions in water.[4]

Asymmetric reactions ‘in water’ are rare. It is a challenge in the field to carry out organic transformations with a high enantiomeric induction in aqueous system. Asymmetric Aldol reactions which catalysed ‘in presence of water’ can be carried out using emulsification technique (water in oil, w/o). This can be achieved by introducing amphiphilic property in the proline moiety (Fig. 6).

1.6 Strategy of using Fatty Acids with L-proline

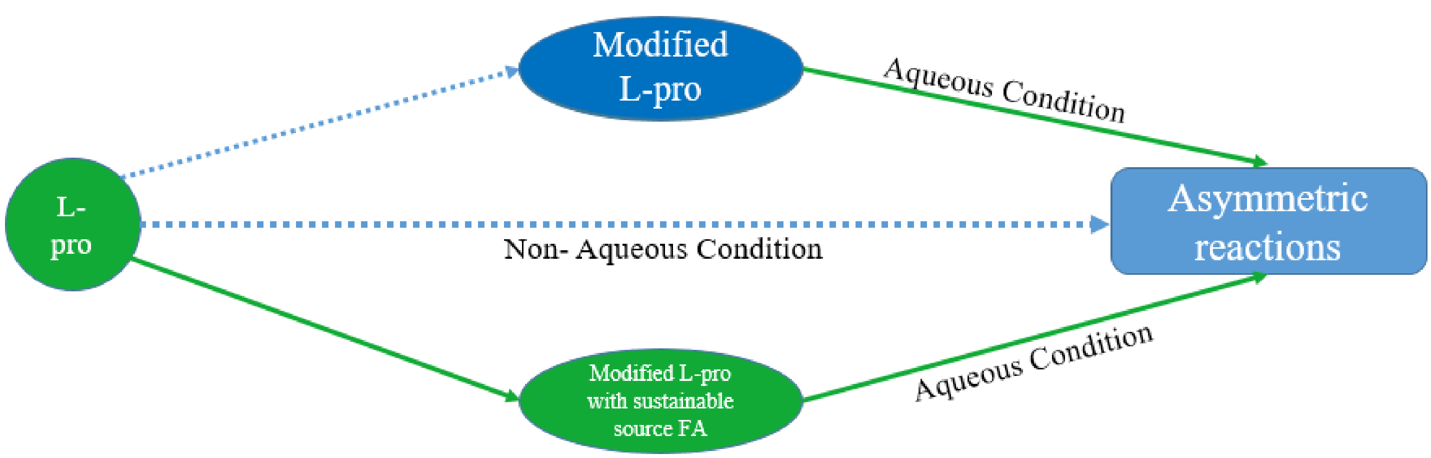

Fig. 7. Strategy of fusion of unsaturated fatty acids (FA) with the organocatalyst L-proline (L-pro).

L-proline is the versatile green sourced organocatalyst, but it needs to be modified for the heterogeneous system, especially for aqueous reaction conditions (Fig.7). Mostly, it is modified with the petroleum based organic bulky reagents by multistep processes for the requirement of steric environment in the catalytic molecule. Our strategy to replace this petroleum based organic reagents with green sourced chemicals (like oleochemicals) with fulfilling the purpose of heterogeneity for the aqueous condition and steric environment for the better enantioselectivity. For sustainable solution, biomass is one of the most preferred sustainable source for chemicals and fuels. Oleochemicals (contains fatty acids, fatty alcohols, fatty amines, fatty esters, glycerine) are derived from plants and animals. They are sustainable building blocks for a large variety of chemicals that can be applied as high value starting materials in various industries such as food, pharmaceuticals, cosmetics, bio-refineries, plastics, and many others (Fig. 8).

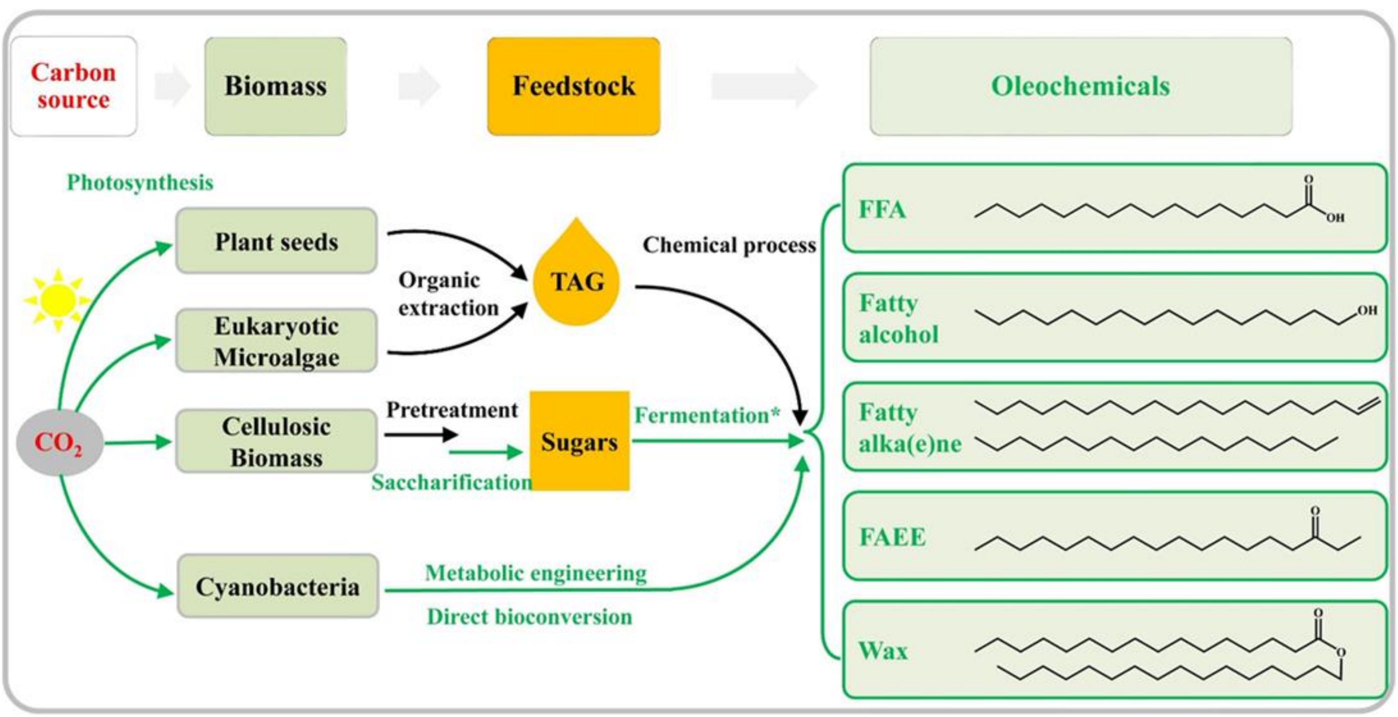

Fig. 8. Overview of both traditional and emerging technologies for the bio-production of oleochemicals.[9]

Fatty acids are categorized in two types: good fatty acids and bad fatty acids. Good fatty acids contains *cis* form of unsaturated hydrocarbon chains. They are essential for human health and for prevention of chronic diseases. Bad fatty acids contains saturated and *trans* form of unsaturated hydrocarbon chains and they are prone to be known for adverse health effect. The biggest issue encountered so far is obtaining a sufficient level of fatty acids in order to meet the continuously increasing world demand for it, taking into account the modern world challenge of looking for sustainable, renewable and cost-effective sources without damaging the marine ecosystem and vegetation.[6]

Microorganisms (microalgae, yeast, fungi, bacteria, and plants) are shown to be remarkable producers of fatty acids. Investigation of chemical biology and genetic-metabolic engineering have become very advanced and efficient tools for researchers to obtain a high yield of fatty acids and lipids. A new path to obtain highly sought-after/high-value fatty acids have been marked with a renewable, green, and low-cost aspect. Design of metabolic engineered cell factories is the way forward to overcome the demand of fatty acids with improving the yield and chemical varieties, also the potential for large-scale production.[6]

1.7 References

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