Diverse Applications and Eco-Friendly Catalysts for Michael Addition Reaction

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Abstract. Michael addition reaction, renowned for its mild reaction conditions facilitated by the absence of small molecule release, has become indispensible in creating numerous substances. It is a focal point in chemical research, fostering avenues for significant advancements. In tandem, the rise of green chemistry has emerged as a pivotal approach in modern chemical research, emphasizing pollution prevention at the source rather than remediation post-contamination. This innovative methodology advocates for developing technologies that substantially mitigate or eliminate waste detrimental to the environment, ensuring that the chemicals synthesized do not negatively impact the ecosystem. This principle has garnered widespread acclaim and utilization among researchers, heralding a new era of environmentally conscious chemical production. This paper meticulously explores the applications of various Michael addition reactions in green chemistry, spotlighting the integration of specialized green catalysts, including enzyme catalysts, in the process. While delineating the multifaceted applications of these reactions, it critically evaluates the current limitations of existing catalysts, thereby setting the stage for prospective research trajectories. As the author delves deeper into this domain, the paper accentuates the necessity to cultivate innovations that amplify the efficiency of these reactions and adhere to the principles of environmental preservation, thus fostering a harmonious balance between scientific progression and ecological sustainability.

Keywords: Michael addition reaction, green chemistry, enzyme catalyst.

1. Introduction

Michael addition is a simple and practical organic synthesis reaction that is thermodynamically controlled. A crucial step in forming a carbon-carbon bond is the Michael addition reaction, a nucleophilic addition reaction with good atomic economy. More significantly, this reaction produces chiral addition products for the most part. As a result, organic synthesis authors have always found the Michael addition reaction to be a fascinating research subject. Komomenos found and reported the first instance of Michael's addition in 1883. He noticed that adding the anion of diethyl malonate to ethyl malonate was simple. The British chemist Arthur Michael did not thoroughly research this reaction until 1887. In 1894, he discovered that electron-deficient triple bonds could function as reaction partners of carbon nucleophiles in addition to double bonds after studying the interactions of stable anions with -unsaturated systems. By the turn of the 20th century, this technique was widely used to create novel carbon-positive ionic connections. The Michael addition reaction has the characteristics of mild reaction conditions; the reaction contains many types of functional groups, reaction monomers can be large or small, and reaction selectivity and conversion are high. In synthesizing straight chain compounds, branched chain compounds, highly branched compounds, dendritic polymers and network polymers, in modifying polymers, biomolecules and synthetic polymer molecules, Michael addition is widely used [1].

Green chemistry involves various fields, such as organic synthesis, catalysis, biochemistry and analytical chemistry. By applying chemical processes and technologies, raw materials, catalysts, solvents, reagents, end products, and by-products that are hazardous to human health, public safety, and the environment are reduced or eliminated. This is known as "green chemistry." Catalysis is gaining more and more attention as an integral component of organic chemistry. With good yield and selectivity, asymmetric Michael addition has been successfully carried out using pyrrolidinone compounds, prolinol silanes, chiral metal complexes, cinchonic base derivatives, polypeptides, and
other catalysts. These catalysts are discovered to be more sensitive to water throughout the use process, and even these catalysts may result in some environmental issues. The use of non-toxic, innocuous, and safe auxiliary compounds, gentle reaction conditions, and reducing the creation of by-products have recently become the current principles for green chemistry due to the promotion of green sustainable development. As a result, many people are interested in employing biocatalysis instead of chemical catalysis in this situation [2,3].

2. Fundamental Mechanism of Michael Addition Reaction

The addition of ethyl acetoacetate to methyl acrylate under base catalysis is one of the most well-known Michael transformations. The mechanism of the reaction is rather simple, with each step being in thermodynamic equilibrium and depending on the kind of acetoacetate and the relative strengths of the bases. As shown in Fig. 1, The base deprotonates the acetoacetate first, producing an equilibrium enolate anion (Michael donor) in the process. The olefin of the acrylate (Michael acceptor) and the enolate anion subsequently interact in a 1,4-conjugate addition. The resultant anion is kept stable by the acrylate's carbonyl until proton transfer takes place, which regenerates the base. The enthalpic change those results from the substitution of an s-bond for a p-bond acts as the general driving factor for conjugate addition. Therefore, 1,4-addition is chosen above 1,2-addition.

However, in some circumstances, assault at the carbonyl carbon rather than the b-carbon of the olefin can be afforded by kinetically regulated reaction conditions. The attack of the enolate anion on the activated olefin is the step that determines the rate. As a result, the reaction rate is first order for the olefin acceptor and the enolate anion and second order for the overall reaction rate. The concentration of the enolate depends on the base strength and the Keq of the active methylene proton's deprotonation. Thus, the base's relative strength and the acetoacetate's composition affect the equilibrium constant [2]．

![Figure 1. General carbon-Michael reaction mechanistic scheme [2]](image)

3. Various Applications of Michael Addition Reaction

3.1. Partial Steps of Synthesis of Batrachotoxin A

As the first application of Micheal reaction, it involves partial steps of synthesizing Batrachotoxin in A (BTX-A). BTX-A is the main synthetic material of Batrachotoxin, known for its high toxicity; it also has high research value. According to Fig. 2, Batrachotoxin can be obtained by simple esterification from A [4]. On the other hand, A is not as toxic, so it is safer to keep. So, scientists usually focus on the synthesis of BTX-A. The overall synthesis is pretty complicated; the paper only focused on the part that involved Michael's reaction. It starts with a Cycloadduct.
As shown in Fig. 3, firstly, TASF is used because F ion can be released in polar solvent (THF/DMF) and can remove TBS from the molecular. As for why this one TBS is falling off, it is further outside the molecule than the other two, so it falls off more easily. The bond formed by F and Si has high bond energy, which is the driving force of the reaction. This is a typical nucleophilic substitution reaction. Fluorine attacks the silicon in the middle, the bond between silicon and oxygen breaks, and electrons are transferred to oxygen, forming oxygen ion, which is one of the conditions for Michael's addition, and then the oxygen ion will attack carbon 1. Then, the double bond between carbon one and carbon two will migrate to carbon 2 and 3, so the electrons from the carbon-oxygen double bond will also be transferred to the oxygen, which will become negatively charged, forming an enolate oxygen ion, leading to the following reaction.

In order to maintain the stability of the enol structure, a new reagent, PhNTf2, was added. The oxygen ion will attack Tf, the bond between one Tf and nitrogen will break, and the Tf will bond with the oxygen (Fig. 4). Finally, the corresponding ester and our target structure will be formed. Overall, Michael's reaction is used to make a seven-membered oxazepane ring. The primary TBS protecting group was removed by treatment with TASF, and the resulting alkoxide attacked the enone at the β-position to afford an enolate as the Michael adduct. The enolate was trapped with phenyl triflimide as the enol triflate [5].

![Figure 2. The comparison between Batrachotoxin in A and Batrachotoxin [5]](image)

![Figure 3. Partial step mechanism of the synthesis of Batrachotoxin in A (Picture credit: Original)](image)

![Figure 4. Partial step mechanism of the synthesis of Batrachotoxin in A (Picture credit: Original)](image)

### 3.2. Carbon Michael Addition Network Prepared by Acetoacetate

Networked polymers produced by the Michael addition reaction have uses in various industries, including coatings, high-performance composites, and drug-delivery devices. Typically, Michael's addition step growth and chain-growth polymerization employing photoinitiated radical or anion processes create such network architectures. Michael's addition is excellent for building well-defined networks due to the commercial availability or simplicity of synthesis of functional oligomers with restricted molecular weight dispersion [1].
Acetoacetate and acrylate precursor, Michael addition networks, have attracted much attention lately. This network structure has drawn much interest because of its comparatively low toxicity and capacity to cure at room temperature without UV light. One of the principals uses for Michael addition networks is in thermosetting coatings that may be applied at room temperature. The Michael addition method has the benefit of not requiring heating or UV light, both of which can damage the substrate and call for extra processing equipment, raising the cost. Due to the malfunction of acetoacetate groups in the industrial process and the absence of unwelcome toxic amines and foul-smelling nucleophilic mercaptans, the addition of alkali-catalyzed acyl acetylated resin carbon Michael to the acrylate receptor is an ideal crosslinking network (Fig. 5). Acrylic monomers and oligomers are excellent choices when creating coatings and adhesives with highly reductive volatile organic compounds (VOCs) and enhancing material characteristics. Photo crosslinked groups in these systems enable tandem Michael addition reactions and free radical polymerization reactions even if UV curing is not required for network creation [1].

![Figure 5](image-url)  
**Figure 5.** Carbon Michael addition polymer prepared by alkali-catalyzed acetylation resin and acrylic ester [1]

### 3.3. Synthesis of Pyroglutamate

A cyclic amino acid called L-pyroglutamic acid (L-PGA) has a carboxyl group attached to the oxygen atom of a ketone. Chiral pyroglutamate and its derivatives are vital substances with significant biological activity that have been extensively researched and used in food, cosmetics, agriculture, medicine, and other fields. Furthermore, pyroglutamate is employed as a precursor in manufacturing natural compounds that can be exploited, including Domoic acid and the neurotoxin anatoxin-a. Therefore, it is crucial to research the production of pyroglutamic acid derivatives and create a novel, practical and effective method for producing pyroglutamic acid and its derivatives [6].

![Figure 6](image-url)  
**Figure 6.** Synthesis of pyroglutamic acid derivatives by Michael addition of acetylene compounds [6]

Lam's research group developed a novel double Michael addition approach for synthesizing multi-substituted pyroglutamic acid derivatives in 2007 [7]. By using an amide-linked carbohydrate 71 and an aromatic alkynyl ketone 70 as substrates in the presence of sub stoichiometric potassium tert-butanol and transition metal salts (Mg (OTf)2 or Ni(acac)2), a series of highly functional pyroglutamic acid derivatives 72 were created (Fig. 6). Metal salts have been discovered to be crucial in increasing the reaction's Dia stereoselectivity.
The Bhat research team published an innovative and useful approach for the mild synthesis of 3-substituted pyroglutamic acid derivatives in 2019 [8]. Through a one-pot multi-component reaction including McGellanate 76, aldehyde 19, and glycine ester Schiff base 77, a 4-carboxy-3-substituted chiral pyroglutamic acid derivative 78 was created (Fig. 7). This innovative one-pot method tolerates a wide range of aldehydes under moderate reaction conditions, including aliphatic aldehydes that can be enolized, without the need for an additional catalyst.

As shown in Fig. 8, a highly efficient method for producing pyroglutamate derivatives is the conjugated addition of alpha-C of glycine imide to alpha, beta-unsaturated molecules followed by hydrolysis/lacamidation, such as: Through a Cu(I)/BINAP catalyzed series Michael addition reaction, Wang’s research team discovered a straightforward procedure for producing chiral pyroglutamic acid derivatives with quaternary stereocenters by adding -substituted iminoester 83 to MBH carbonate 82. A deprotection/lacamidation reaction method is then used to produce the bioactive pyroglutamate derivatives with good yield and outstanding enantioselectivity [9].

![Figure 7. Synthesis of pyroglutamic acid derivatives by multi-component one-pot method [6]](image1)

![Figure 8. Cu(I)/BINAP catalyzed synthesis of chiral pyroglutamate derivatives [6]](image2)

### 4. Green Catalysts

Quinine, also known as cinchona base, is an alkaloid with a very bitter taste, is soluble in ethanol, chloroform, benzene, ether, and other organic solvents, and is only marginally soluble in water. Early on, the principal usage of cinchona base and its derivatives was for medical purposes. It is also frequently employed to catalyze asymmetric organic synthesis because of the molecule's rigidity and chiral active core. One of the concerns of chemists in recent years has been the study of the catalytic asymmetric Michael addition reaction and the production of cinchona base derivatives [10]. In 2007, MCCOOEY et al. first catalyzed the Michael addition reaction of aliphatic aldehydes and ketones with aromatic nitroalkenes using synthesizinchonine derivative 27 as a catalyst and benzoic acid as an assistant [11]. The asymmetric Michael addition reaction was catalyzed by the cubic amide polymer catalyst 31, which was created in 2020 by ULLAH et al. using the cycloidiene complex decomposition reaction and Hoveyda-Grubbs second-generation catalyst [12]. The study revealed that all 31 polymer catalysts had good catalytic activity. However, although the catalyst activity is high, the synthesis method of the catalyst is more ingenious, but the synthesis process is more complicated, and the transition metal ruthenium complex special catalyst is used.
Due to the presence of both amino and carboxyl groups in its structure, proline can satisfy the deprotonation conditions necessary for the asymmetric Michael addition reaction and provide carboxyl groups that can form hydrogen bonds and their chiral center. Additionally, altering and adjusting the functional group can increase the substrate's application range, making it advantageous [13]. In 2017, MONDAL et al. created the proline derivative catalyst 22, which was utilized to catalyze the Mical-Aldol addition reaction of various substituted cinnamaldehydes and-arylpyrazolone to produce spiro compounds [14]. With acetic acid as an additive and a catalyst with a 10% molar fraction, the reaction was conducted in a dichloroethane solution. The greatest yield was 98%, and the ee value was higher than 99% when the reaction was run at 30°C for 12 hours. The authors hypothesized that the catalyst generated an imine with unsaturated aldehydes, followed by a Vinylogous Michael addition reaction with -arylpyrazolone before the Aldol reaction occurred inside the molecule. This is how the Michael-Aldol addition was allegedly catalyzed by Accelerator 22. formed a compound in a spiral. Because the protamine molecule retains the catalytic active center of proline, it has good catalytic performance for the Michael addition reaction [10].

A blend of one aminopeptidase and at least three casein enzymes make up streptomyces griseus protease. The casein enzymes were identified as Streptomyces griseus trypsin, Streptomyces griseus protein A, and Streptomyces griseus protease B. Streptomyces griseoymes proteases were used by Zhang to study the Michael addition reaction between n-subsituted maleimide and 1, 3-dicarbonyl compounds [3]. By improving the reaction conditions, the ideal enzyme environment was created. The ideal reaction environment also increased the substrate's applicability, leading to a medium to outstanding yield and specific Dia stereoselectivity. 91% was the greatest yield, and 99/1 was the best dr Value. A total of 25 compounds are produced using the catalyst, 18 of which are novel compounds. The catalyst has high universality. This reaction increases the variety of enzymatic catalysis applications by offering a sustained catalytic method for organic synthesis.

5. Conclusion

It can be seen from the research overview of the Michael reaction that many cutting-edge topics in today's world are based on the Michael reaction, and the study of catalytic asymmetric Michael addition reaction is particularly prominent, which shows the importance of Michael addition reaction in the field of organic synthesis research. In addition, green chemistry is an inevitable trend in the development of modern chemistry and an important part of sustainable development. The international research on Michael's reaction has been extensive and in-depth, focusing on its catalyst and the mainstream use of organic small molecule catalysts.

Enzymatic catalysis and microwave-assisted catalysis, as new catalytic methods, will become research hotspots in the future. However, these new catalysts still have shortcomings, such as high production cost, cumbersome preparation process, relatively narrow trial range of substrates, difficult recovery and utilization of catalysts or inactivation of recovery catalysts, and low utilization rate of catalysts, which limit their large-scale production and application. Therefore, future research focuses on designing more efficient, green and stable catalysts for the Michael addition reaction. However, these new catalysts still have some drawbacks, restricting their use and large-scale production. These drawbacks include high production costs, laborious preparation procedures, a relatively small trial range of substrates, challenging catalyst recovery and utilization or inactivation of recovery catalysts, and low catalyst utilization rates. Future research will thus concentrate on creating Michael addition reaction catalysts that are more effective, environmentally friendly, and stable.

References


