Exploring Strychnine from Synthesis and Reaction Mechanisms

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Abstract. Strychnine is a prominent organic compound with significant impacts in both organic synthesis and pharmaceuticals. This article provides a detailed account of various synthetic methods employed to produce strychnine over different decades, categorizing them into the 1950s-1960s, 1990s-2000s, and the modern era. It critically assesses the advantages and disadvantages of each synthetic approach within these time frames, with a particular focus on four advanced methods of recent times: transition-metal catalyzed synthesis, asymmetric synthesis, and biocatalysis synthesis. Furthermore, this review delves into the synthetic principles underlying these methods and examines their potential for achieving controlled synthesis reactions. The positive ramifications of controlled synthesis methods are explored in depth, encompassing areas such as education, synthetic reactions, criminal investigations, and pharmaceutical development. However, the research finds that each modern synthetic method still faces its own set of challenges, including issues related to reaction instability, scale limitations, and stringent reaction conditions. Consequently, researchers must dedicate extensive efforts to address these problems in order to realize the potential of controlled synthesis methods.

Keywords: Organic incense, Agarwood, chemical component, human health.

1. Introduction

Strychnine alkaloid, determined by chemists Joseph Bienaimé Caventou and Pierre-Joseph Pelletier from France in 1818, has played a significant role in criminal cases throughout history due to its distinctive chemical and physical properties [1]. It is a hypertoxic, colorless crystalline substance. Strychnine has been known for its toxicity and medicinal properties since ancient India, where it is found in plants belonging to the Strychnos genus, particularly in Strychnos nux-vomica and ignatii, which are native to Southeast Asia countries. It was discovered as the first alkaloid in plants of the Strychnos genus, which is in the Loganiaceae family. Strychnine has also had a notable impact and exploratory value in the medical and organic chemistry fields. In the medical field, it has been used since as early as 1640 to kill small vertebrates and was employed by the Dirlewanger Brigade for biochemical warfare during World War II. When ingested in certain quantities through methods such as oral consumption, inhalation, or injection, it stimulates the central nervous system, leading to convulsant effects, often resulting in severe muscle spasms, seizures, and even death. Furthermore, it was popularly used as a performance enhancer in the 19th and early 20th centuries. For instance, an infamous incident involving its utilization occurred during the 1904 Olympic marathon, wherein the track-and-field competitor Thomas Hicks received a mixture of egg whites and brandy infused with a small quantity of strychnine from his support crew to enhance his endurance. Hicks emerged victorious in the race; however, he encountered hallucinations and succumbed to exhaustion shortly after completing the race. Apart from its poisonous properties, controlled and precise administration of limited strychnine amounts has been historically employed to enhance the functioning of the central nervous system as a therapeutic intervention. In the field of organic chemistry, its complex structure has made it a highly challenging and valuable research subject [2-5].

Discovering and improving the total synthesis of strychnine has been a milestone achievement in organic synthesis, attracting the attention of numerous chemists. In 1946, its structure was first defined by Sir Robert Robinson, revealing its intricate giant molecular structure, comprising multiple

rings, carbon atoms, and functional groups. Its synthesis has always been a landmark challenge, and the initial complete synthesis of strychnine was documented by the scientific team led by R.B. Woodward in 1954. As of now, there are more than ten well-established synthetic methods. Over more than half a century of chemical research, researchers have continually utilized its unique structural features to develop new synthetic methods and explore its potential similarities with other complex macromolecules. This article will delve into the exploration and improvement of strychnine synthesis methods in different eras, exploring the chemical complexity of strychnine and its unique position in the history of organic synthesis. Furthermore, it is necessary to investigate how to achieve better-controlled synthesis methods and how these methods can enhance the application of strychnine in the future, as well as the potential changes in the landscape of future synthetic chemistry [6-8].

2. Mechanisms in Different Ages

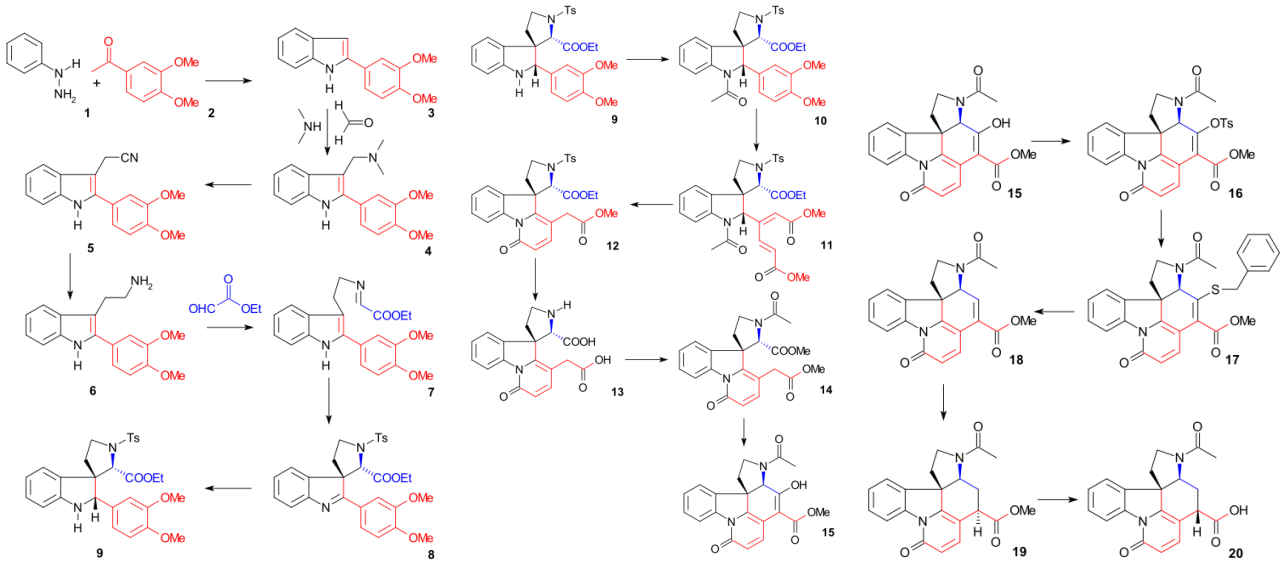

Figure 1. Synthesis mechanism by Woodward, reproduced from the website: https: //en.wikipedia.org/wiki/Strychnine_total_synthesis#Ring_II, _V_synthesis.

Woodward began by breaking down the complex strychnine molecule into simpler, more readily available precursors in 1954. He identified two major fragments: the indole moiety and the cycloheptadiene ring. Next, Woodward started with the synthesis of the indole fragment, a critical component of strychnine. He achieved this by condensing tryptamine and phenylhydrazine, followed by a series of reactions to construct the indole ring. Woodward designed a unique strategy to construct the cycloheptadiene ring, using a Diels-Alder reaction between an appropriately functionalized diene and a dienophile. After obtaining the key fragments, Woodward employed a series of reactions to assemble them into the strychnine structure. These reactions included oxidation, reduction, and protection/deprotection steps. The final steps involved completing the remaining functional group transformations and removing protecting groups to yield strychnine (Fig. 1).

Philip Magnus's 1992 synthesis of strychnine marked a seminal achievement in the field of organic chemistry. This groundbreaking work demonstrated an intricate and highly efficient route to produce strychnine. Magnus's synthesis showcased innovative strategies and novel reactions, pushing the boundaries of synthetic chemistry. This milestone not only contributed to our understanding of organic synthesis but also held significant implications for medicinal chemistry and pharmacology, as strychnine has been historically studied for its intriguing neurotoxic properties. Magnus's achievement remains a testament to the ingenuity and advancement of synthetic chemistry in the early 1990s.

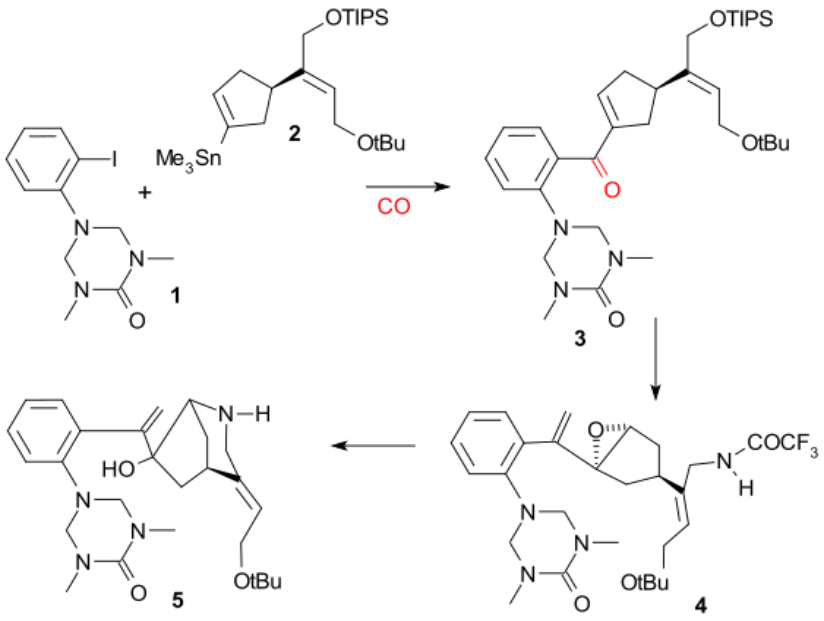

Figure 2. Overman synthesis mechanism, reproduced from the website: https: //en.wikipedia.org/wiki/Strychnine_total_synthesis#Ring_II, _V_synthesis.

In 1993, Dale L. Boger and Samuel J. Danishefsky achieved a remarkable milestone in organic chemistry with their groundbreaking synthesis of strychnine. This intricate and innovative synthesis not only provided a highly efficient route to the structurally complex alkaloid but also showcased the cutting-edge strategies and methodologies employed by the researchers. Strychnine had long posed a formidable challenge to synthetic chemists. The successful synthesis by Boger and Danishefsky not only expanded the horizons of synthetic organic chemistry but also had profound implications in medicinal chemistry, highlighting their exceptional contributions to the field.

In the 1993 Keuhne synthesis, racemic strychnine was synthesized starting with tryptamine and 4,4-dimethoxy acrolein. These compounds underwent a series of transformations: an amine-carbonyl condensation facilitated by boron trifluoride and a sigmatropic rearrangement to form an acetal. After perchloric acid hydrolysis, an aldehyde was obtained. The aldehyde was then converted into an epoxide via a Johnson–Corey–Chaykovsky reaction, which subsequently reacted in situ with a tertiary amine, yielding an ammonium salt along with impurities. The following steps involved benzyl group removal, leading to an alcohol, followed by reduction using sodium cyanoborohydride and acylation, resulting in a mixture of epimers at C17. The closure of rings III and onwards was achieved through an aldol reaction, utilizing only the appropriate epimer.

Further reduction and acylation led to di-acetate epimers. Subsequent reactions included elimination mediated by DBU to form an olefinic alcohol, Swern oxidation resulting in the formation of an unstable amino ketone, and a Horner–Wadsworth–Emmons reaction yielding an acrylate ester. A photochemical rearrangement ensured the desired (trans) configuration, followed by reduction to yield is strychnine. Finally, racemic strychnine was obtained through a base-catalyzed ring closure. In the 1998 Keuhne synthesis of chiral (−)-strychnine, they employed a chiral starting material derived from tryptophan.

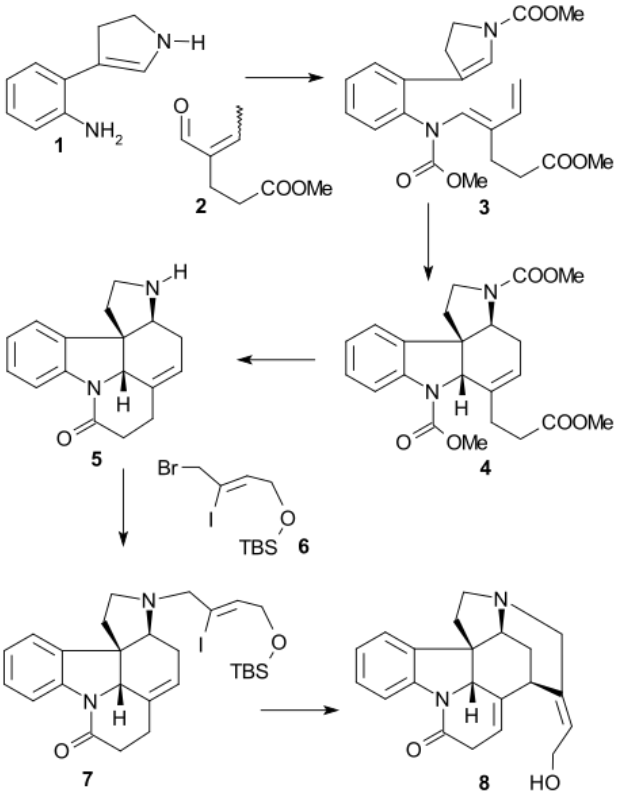

Figure 3. Synthesis mechanism by Rawal, reproduced from the website: https: //en.wikipedia.org/wiki/Strychnine_total_synthesis#Ring_II, _V_synthesis.

In Rawal's synthesis of racemic strychnine in 1994, amine and enone were subjected to an amine-carbonyl condensation reaction, followed by quenching with methyl chloroformate, resulting in the formation of triene. A Diels–Alder reaction conducted in benzene at 185°C produced hexene. By employing iodotrimethylsilane, the hydrolysis of three ester groups was accomplished through seven reaction steps, including a Dieckmann condensation, ultimately yielding pentacyclic lactam. The addition of the C4 segment via amine alkylation and Heck reaction led to the production of is strychnine after TBS deprotection. This method achieved the highest overall yield (10%) among the published approaches.

In the 1999 chiral Bosch synthesis, dione underwent ozonolysis, converting the olefin group into an aldehyde, followed by a double reductive amination involving chiral amine. The phenylmethyl group was subsequently removed, and an enone group was introduced to form carbamate. Subsequent steps included deprotection, alkylation, reductive Heck reaction, methoxy carbonylation, and zinc-induced transformations, resulting in the formation of the tetracyclic compound. The final stages involved the conversion to Wieland-Gumlich aldehyde through NaH treatment and DIBAH reduction of the methyl ester.

In the 2000 racemic Vollhardt synthesis, a pivotal step entailed the alkyne trimerization of a tryptamine derivative, utilizing acetylene and CpCo $(C_2H_4)_2$, which yielded a tricycle. Subsequent reactions involved [1,8]-conjugate addition, amine alkylation, and isomerization of the diene system to produce none. A Heck reaction was employed to synthesize pyridone, and reduction with lithium aluminum hydride, followed by TBS group deprotection, culminated in the formation of is strychnine.

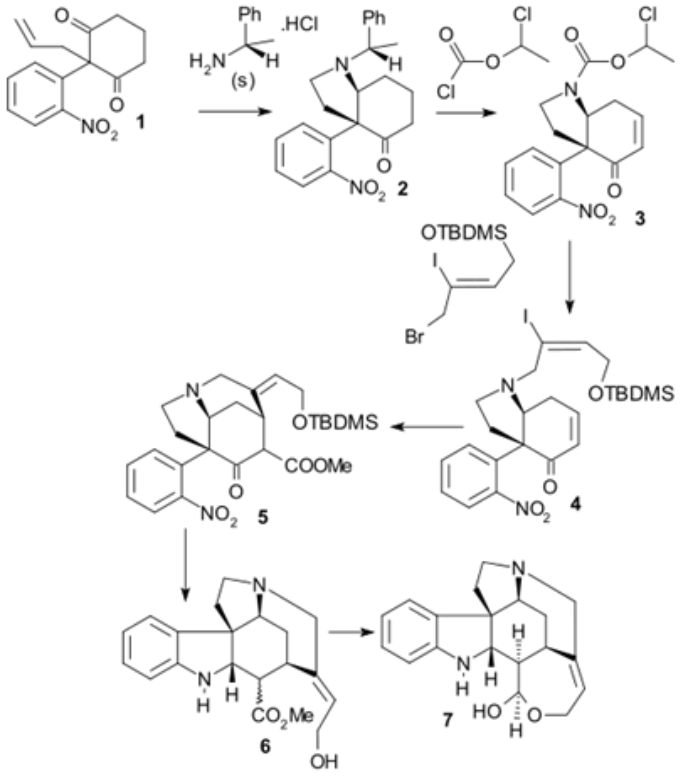

Figure 4. Synthesis mechanism by Mori, reproduced from the website: https: //en.wikipedia.org/wiki/Strychnine_total_synthesis#Ring_II, _V_synthesis.

The 2003 Mori synthesis of (-)-strychnine marked a milestone by incorporating the first asymmetric reaction step. It relied extensively on palladium-catalyzed reactions. Beginning with N-tosyl amine, an allylic asymmetric substitution was achieved with allyl carbonate, utilizing $Pd_2(dba)_3$ and the asymmetric ligand (S-BINAPO) to produce chiral secondary amine. Desilylation of the TBDMS group, followed by a series of transformations through HCl, hydroxide, bromide, and nitrile formation, yielded the compound. Subsequent Heck reaction and debromination steps led to the tricycle. Further reactions involved nitrile reduction, Boc protection, and second allylic oxidation, resulting in tetracycle. Additional processes included hydroboration-oxidation, Swern oxidation, enol triflate formation, and triflate removal to yield alkene. Detosylation, amidation, and another Heck reaction formed pentacycle. Double bond isomerization, Boc deprotection, amine alkylation, and a final Heck reaction ultimately yielded (-)-isostrychnine.

In the 2002 Shibasaki synthesis of (-)-strychnine, a pivotal asymmetric Michael reaction occurred between cyclohexenone and dimethyl malonate, catalyzed by AlLibis(binaphthoxide) to yield chiral diester. The ketone group was acetal-protected (2-ethyl-2-methyl-1,3-dioxolane, TsOH), and a carboxyl group was removed (LiCl, DMSO 140°C) to form a monoester. The addition of a C2 fragment as Weinreb amide led to PMB ether. Further transformations included ketone reduction, water elimination, ester reduction, and TIPS protection, followed by acetal group removal to obtain ketone. Enone was synthesized via Saegusa oxidation. Alcohol was formed through a Mukaiyama aldol addition, followed by iodonation and a Stille coupling to introduce the nitrobenzene unit, yielding compound. Alcohol was achieved after SEM protection and TIPS removal, followed by a series of reactions to yield the compound. Further steps included imine reduction, acylation, deprotection, and re-protection, eventually leading to (+)-diaboline, which is acylated to form the Wieland-Gumlich aldehyde.

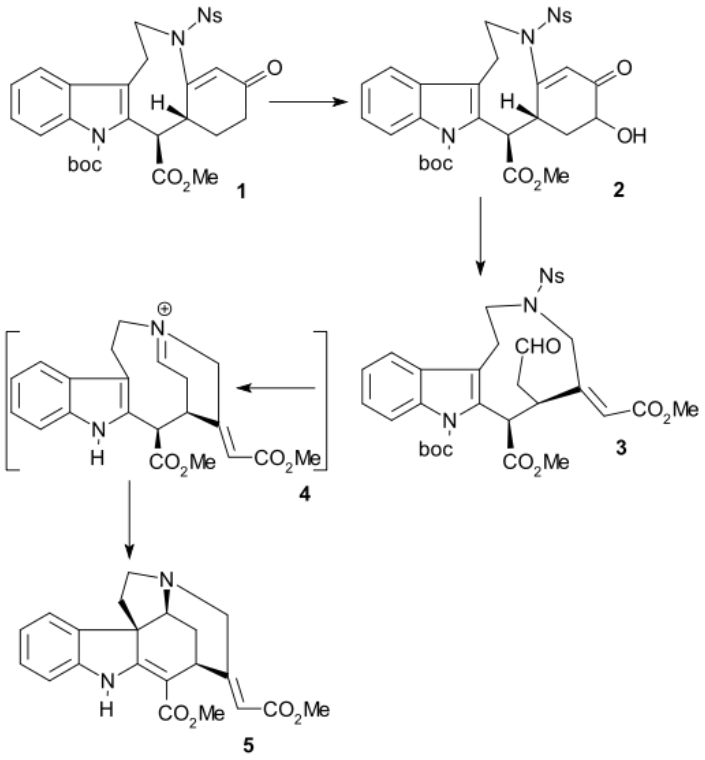

Figure 5. Synthesis Mechanism by Li, reproduced from the website: https: //en.wikipedia.org/wiki/Strychnine_total_synthesis#Ring_II, _V_synthesis.

The 2002 Bodwell/Li synthesis, a formal synthesis, replicated a compound previously prepared by Rawal. The pivotal step involved an inverse electron-demand Diels–Alder reaction of cyclophane, followed by the reduction of the double bond to form a compound using sodium borohydride and triflic acid, along with carbamate group removal to yield the compound. However, the method is contentious, as challenged by Reissig. In the 2004 Fukuyama synthesis of chiral (-)-strychnine, the process commenced with cyclic amine, where chirality was introduced via enzymatic resolution. Acyloin was obtained through Rubottom oxidation and hydrolysis. Lead acetate oxidative cleavage generated aldehyde, followed by nosyl group removal (thiophenol/cesium carbonate). This led to an amine-carbonyl condensation with iminium ion, facilitating a transannular cyclization to produce diester. Finally, the diester could be transformed into the Wieland-Gumlich aldehyde using established chemical reactions.

The 2010 Beemelmanns & Reissig synthesis, a formal one, aimed to produce Rawal's pentacycle (amine in Rawal's method). Indole underwent a single cascade reaction with samarium diiodide and HMPA to form a tetracycle. Raney nickel/H2 reduction yielded amine. A one-pot reaction led to Rawal precursor, ensuring key hydrogen atoms were in the desired anti-configuration. In an abandoned route, the intermediate was reduced to imine, converted to carbamate, dehydrated to diene (Burgess reagent), and reduced to, but with undesired cis hydrogen atoms, differing from Bodwell/Li's 2002 results. In 2011, the Vanderwal group achieved a remarkably short, six-step total synthesis of strychnine. Their approach included a Zincke aldehyde, an anionic bicyclization reaction, and a tandem Brook rearrangement combined with a conjugate addition, streamlining the complex synthesis process for strychnine.

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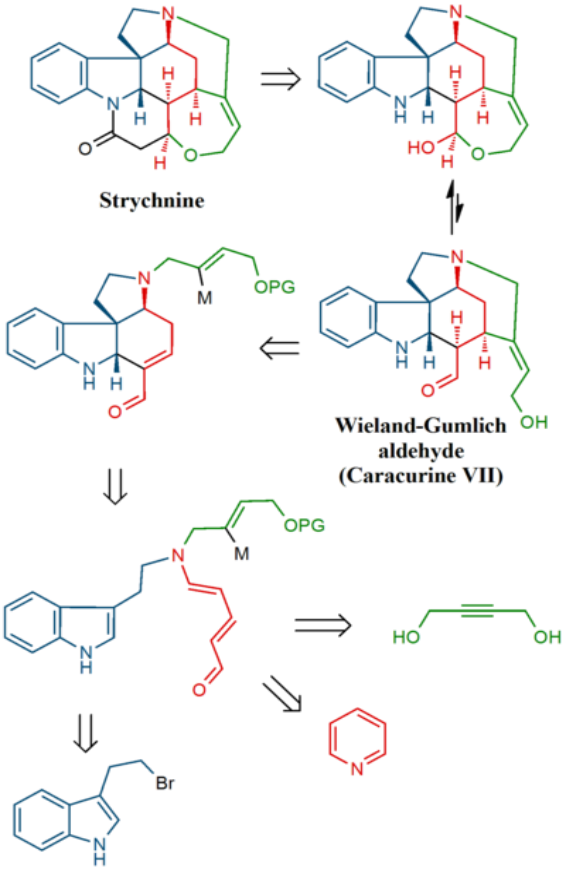

Figure 6. Synthesis mechanism, reproduced from the website: https: //en.wikipedia.org/wiki/Strychnine_total_synthesis#Ring_II, _V_synthesis.

3. Progress of Development of Synthesis Methods

3.1. Classic Organic Synthesis: 1950s-1960s

Chemists usually use classic organic synthesis methods, involving a series of chemical reactions starting from simpler starting materials. These methods give the basic reaction principle, which helps people to understand the complex organic reaction. These methods usually require multiple steps, and their total yields are always less than 1%, making the process inefficient and costly. In addition, the generation of hazardous by-products and waste cause environmental problem.

3.2. Modern Organic Synthesis: 1990s-2000s

With improvement, chemists use modern synthesis, such as transition metal-catalyzed reactions. These methods offer shorter and more efficient synthesis pathways, which enhance synthesis and output efficiency, thereby increasing economic feasibility. Some of these methods still need some special starting materials, limiting them to a large scale and raising the cost. Moreover, the generation of products that cause an environmental problem also causes issues.

3.3. Advanced Synthetic Methods: Present Day

In recent years, advanced synthetic methods represented by asymmetric synthesis and biocatalysis have been used in the synthesis of strychnine. Asymmetric synthesis methods have improved selectivity, allowing for the manufacturing of specific enantiomers of strychnine. Biocatalysis approaches have shown promise in utilizing enzymes for selective reactions, decreasing the need for harsh chemical reagents. Both synthesis methods can be technically challenging and may require specialized knowledge and equipment in manufacturing. The cost-effectiveness and scalability of these methods on an industrial scale are still a problem.

3.4. Summary

To sum up, the development of strychnine synthesis techniques is influenced by various factors such as efficiency, safety and environmental pollution. As synthetic technology continues to advance, modern advanced techniques have significantly enhanced synthetic efficiency and have also started to address environmental pollution issues to some extent. However, correspondingly, their application on a large scale poses ongoing challenges, and economic costs are increasing. In the future, the key focus will be on further improving asymmetric synthesis and biocatalysis synthesis methods.

4. Importance and Method of Controllable Synthesis

4.1. Significance

The controllable synthesis of strychnine will influence several aspects [9]. As a large organic compound with a complex synthesis process, a controllable synthesis method can provide a number of valuable insights into fundamental principles of organic chemistry, which help researchers use this experience on other organic research compounds. Strychnine contains highly toxic properties, so it has the potential to invent new types of analogs or derivatives. Moreover, it provides some valuable opinions on solutions to other toxic substances with the same principle. Besides, it also can aid in the discovery of new drugs due to their therapeutic effect in pain management or neurological disorders. Strychnine, due to its high toxicity and easy availability on the market, is often used in some murder cases. Mastering controllable synthesis methods can help forensic experts quickly and reliably determine the cause of death, thereby improving the efficiency of solving cases. As a milestone in natural product synthesis, proficiently mastering the synthesis of strychnine can place it in chemistry education as a classic example of reaching synthetic reactions, including important concepts like stereochemistry and multi-step synthesis [10, 11].

4.2. Transition-Metal Catalyzed Synthesis

In general, transition metals, which are metals located in the d-block of the periodic table, are often employed as catalysts in synthetic reactions to enhance the efficiency of converting reactants into desired products. This method is often used in conjunction with various other types of reactions, including oxidative addition, reductive elimination, ligand coordination and so on, and it reduces costs by utilizing the catalyst's recyclability feature.

Firstly, transition-metal catalysts can activate a wide range of organic substrates by coordinating with them. This coordination weakens the bonds within the substrate, making it more reactive and prone to participating in chemical reactions. Common modes of substrate activation include oxidative addition, migratory insertion, and coordination to the metal center. Secondly, controlled Reaction Pathways: Transition metals can influence the course of a chemical reaction by directing the flow of electrons and stabilizing key intermediates. This control allows for the selective formation of desired products, even in the presence of multiple reactive sites within a molecule. Thirdly, Transition-metal catalysis typically involves a catalytic cycle, where the metal catalyst undergoes a series of reversible transformations. The cycle usually includes substrate binding, activation, reaction, and product release. Importantly, the catalyst remains largely unchanged throughout the cycle, making it an efficient and sustainable process. Finally, Chemo-, Regio-, and Stereoselectivity: Transition-metal catalysts often exhibit remarkable selectivity in promoting specific reactions. They can differentiate between different functional groups (chemo selectivity), choose specific positions within a molecule for reaction (regioselectivity), and control the spatial arrangement of substituents (stereoselectivity), leading to the synthesis of complex molecules with high precision.

4.3. Cyclization Reaction Synthesis

Cyclization reaction is necessary for the formation of a wide range of cyclic compounds from small(3-7membered) to big rings(8+membered), which make it often used to build complex organic

molecules by particular positions of reactive groups and conditions. Besides, it is frequently employed in the synthesis of natural products, such as alkaloids, terpenes and polyketides, to copy their structural complexity. The central principle of cyclization reactions is the formation of a covalent bond between two atoms within the same molecule to create a cyclic structure. This bond formation typically involves breaking one or more existing bonds within the reactant molecules.

Cyclization reactions can lead to the formation of rings of various sizes, ranging from small rings (3-7 membered) to large rings (8+ membered). The choice of ring size often depends on the desired product and the reactivity of the starting materials. Cyclization reactions can proceed through various mechanisms, including nucleophilic addition, electrophilic addition, radical reactions, and transition metal-catalyzed processes. The choice of mechanism depends on the nature of the reactants and reaction conditions. Cyclization reactions can be highly regioselective and stereoselective. Chemists must carefully design the reaction conditions and reactant structures to control which bonds are formed and the relative orientation of substituents in the resulting cyclic product.

4.4. Asymmetric Synthesis

Asymmetric synthesis, also known as chiral synthesis, refers to a chemical reaction in which an initially achiral component within a group of substrate molecules is transformed into a chiral component, resulting in the production of unequal quantities of stereoisomers. It is significant in the pharmaceutical, agrochemical and fine chemical industries, where the biological activity of a compound often depends on its chirality. One of the fundamental principles of asymmetric synthesis is to begin with chiral starting materials or substrates. These starting materials can be natural products, chiral reagents, or synthetically derived chiral building blocks. The chirality in the starting material serves as a source of asymmetry in the final product.

Asymmetric synthesis often involves the use of chiral catalysts. Chiral catalysts are molecules that can selectively facilitate chemical reactions in a way that favors the formation of one enantiomer over the other. They do this by interacting with the reacting molecules in a stereospecific manner. Common types of chiral catalysts include chiral ligands in transition metal-catalyzed reactions and enzymes in biocatalysis. Achieving stereochemical control is a key principle in asymmetric synthesis. This involves designing and optimizing reaction conditions to ensure that the desired stereoisomer is formed in high yield and selectivity. Factors like temperature, solvent, concentration, and reaction time can be carefully manipulated to influence the stereochemistry of the reaction. Enantioselective reactions are those that preferentially produce one enantiomer of the product. This selectivity can be achieved through the use of chiral catalysts, chiral auxiliaries, or other chiral reagents. Enantioselective reactions are at the heart of asymmetric synthesis and are used to create a wide range of chiral compounds.

4.5. Biocatalysis Synthesis

In the realm of green chemistry, biocatalysis offers numerous advantages when compared to chemo catalysis. These advantages encompass gentle reaction conditions, typically operating under physiological pH and temperature ranges, the employment of environmentally friendly catalysts in the form of enzymes, as well as compatible solvents, primarily water. Biocatalysis boasts exceptional catalytic activity and demonstrates impressive regio- and chemo-selectivities, particularly when dealing with multifunctional molecules. Consequently, the utilization of enzymes can obviate the necessity for functional group activation or the unwarranted inclusion of protection and deprotection steps. Enzymes are incredibly specific in their interactions with substrates. Each enzyme has a well-defined active site that accommodates specific molecules, ensuring that reactions occur with high selectivity and minimal side reactions. This specificity is crucial for the synthesis of complex molecules with precise stereochemistry.

Biocatalysts exhibit remarkable selectivity in terms of the chemistry they catalyze (chemo selectivity), the position of a reaction within a molecule (regioselectivity), and the spatial arrangement of products (stereoselectivity). This level of control is often challenging to achieve with traditional

chemical catalysts. Biocatalysis generally operates under mild conditions, such as physiological temperatures and neutral pH levels. This is in stark contrast to many traditional chemical reactions that require harsh conditions and generate toxic waste products. Mild conditions are not only environmentally friendly but also preserve the stability of sensitive compounds. Biocatalysts can often work with biologically derived substrates, making them well-suited for the production of pharmaceuticals, biofuels, and other bioproducts. This compatibility with biological systems can lead to more efficient and cost-effective processes. Immobilizing enzymes on solid supports or within matrices can enhance their stability and reusability, making biocatalysis more economically viable for large-scale industrial applications.

5. Conclusion

In summary, this article, through an analysis of the history of strychnine synthesis and studies on the synthesis reaction mechanisms in different years, as well as a classification analysis of synthesis methods from various eras (from 1954 to 2011), has identified the advantages and disadvantages of various synthesis methods. Additionally, during the exploration of the principles behind these synthesis methods, future research directions for achieving controlled synthesis methods were discovered. People need to improve current synthesis technologies in multiple directions, such as practicality safety, creating more straightforward reaction environments and processes, production efficiency, and reducing environmental pollution.

Simultaneously, the importance of controlled synthesis methods is discussed in the article. The implementation of this method will have far-reaching positive impacts in various fields, including organic synthesis, forensic analysis, chemical education, pharmaceutical development, and more. Specifically, it can assist researchers in gaining experience to study other organic compounds, serve as important reactions for teaching chemistry, including stereoselective synthesis, aid forensic investigations in eliminating homicide factors, or contribute to the research of new drugs in the fields of pain management or neurological disorders. For the future, perhaps the research should focus more on improving various aspects of strychnine synthesis, including production efficiency, safety, environmental pollution, cost, and a simpler synthesis process. At the same time, further research and exploration in new directions in the synthesis field are also necessary. For example, ensuring the stability of asymmetric synthesis and reducing the economic costs of biocatalysis synthesis are important areas to explore.

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